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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	James U. Morrison	)
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Serial No:	09/829,707	)
		)
Filed:	April 10, 2001	)
		)
Title:	Method and Composition for Controlled Release Acarbose Formulations	)
		)
Art Unit:	1623	)
		)
Examiner:	Everett White	)
		)

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

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This is an appeal from the Examiner's final rejection of the claims in the above-identified application (Ex. 1).

The fees required under 37 C.F.R. § 1.17 are dealt with in the accompanying Fee Transmittal Form.

The brief is filed in triplicate (37 C.F.R. § 1.192(a)).

I. JAMES U. MORRISON IS THE REAL PARTY IN INTEREST (37 C.F.R. § 1.192(c)(1))

James U. Morrison is the sole inventor of the subject application and is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES (37 C.F.R. § 1.192(c)(2))

None

III. STATUS OF CLAIMS (37 C.F.R. 1.192(c)(3))

A. The status of the claims in the application are:

Claims 1-14 and 28-42 were canceled.

Claim 43 was rejected under 35 U.S.C. § 102(a).

Claims 15-27 were rejected under 35 U.S.C. § 102(e).

Claims 15-27 were rejected under 35 U.S.C. § 102(b).

B. Claims on appeal are:

Claims 15-27 and 43 (attached as Appendix A).

IV. STATUS OF AMENDMENTS (37 C.F.R. 1.192(c)(4))

The Examiner stated in the final Office Action dated August 7, 2003 that Applicant's Amendment has been entered. (Ex. 2, pg. 2).

V. SUMMARY OF INVENTION (37 C.F.R. 1.192(c)(5))

The application is directed to the novel composition of acarbose and a sustained release matrix. Acarbose inhibits glucosidase, an enzyme which breaks down complex carbohydrates into glucose. This composition provides for the constant and controlled release of acarbose in the small intestine, where acarbose exerts its therapeutic activity. A controlled and constant rate of release of acarbose in the small intestine results in the constant inhibition of glucose absorption in the small intestine. Evidence of the constant and controlled release of acarbose directly resulting from the novel composition of acarbose and a sustained release matrix is found in the resulting weight loss experienced by patients receiving the composition.

VI. ISSUES (37 C.F.R. 1.192(c)(6))

1. Whether claim 43 is unpatentable under 35 U.S.C. § 102(a) over Rosner et al., U.S. Patent No. 6,387,361 (Ex. 3).

2. Whether claims 15-27 are unpatentable under 35 U.S.C. § 102(e) over Patel et al., U.S. Patent No. 6,309,663 (Ex. 4).

3. Whether claims 15-27 are unpatentable under 35 U.S.C. § 102(b) over Bremer et al., U.S. Patent No. 5,643,874 (Ex. 5).

VII. GROUPING OF CLAIMS (37 C.F.R. 1.192(c)(7))

A. Grouping Of Claims For The Rejection Under 35 U.S.C. § 102(a).

Claim 43 stands alone as far as the patentability of its subject matter is concerned in view of Rosner et al., U.S. Patent No. 6,387,361.

B. Grouping Of Claims For The Rejection Under 35 U.S.C. § 102(e).

Claims 15-27 stand together as far as the patentability of their subject matter is concerned in view of Patel et al., U.S. Patent No. 6,309,663.

C. Grouping Of Claims For The Rejection Under 35 U.S.C. § 102(b).

Claims 15-27 stand together as far as the patentability of their subject matter is concerned in view of Bremer et al., U.S. Patent No. 5,643,874.

VIII. ARGUMENT

A. Claim 43 is Novel and the Rejection Under 35 U.S.C. § 102(a) Is Improper (Arguments Under 37 C.F.R. 1.192(c)(8)(iii))

The Examiner rejected claim 43 under 35 U.S.C. § 102(a) as being anticipated by Rosner, U.S. Patent No. 6,387,361 (hereafter "Rosner"). The Examiner asserted that Rosner discloses a method of controlling weight in a human comprising administering to the human acarbose at meals with food containing carbohydrate, which anticipates the method of instant claim 43. (Ex. 2, pg. 2, ¶ 5).

1. Rosner is not Prior Art Under 35 U.S.C. § 102(a).

Under 35 U.S.C. § 102(a), a person shall be entitled to a patent unless "the invention was known or used by others in this country, or patented or described in a printed publication in this

or a foreign country before the invention thereof by the applicant for a patent...." 35 U.S.C. § 102(a). A patent reference becomes available when published or issued. MPEP § 2126.01. Since the Rosner application did not publish, it became enforceable when issued, i.e., May 14, 2002. Therefore under § 102(a), Rosner is available as a reference as of May 14, 2002. The filing date of the present application is April 10, 2001. It is clear that the filing date of the present application precedes the date Rosner is available as a reference under § 102(a). As such, Rosner cannot anticipate claim 43 under 35 U.S.C. § 102(a) .

2. Rosner does not Disclose an Acarbose Formulation.

A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference. MPEP § 2131. Applicant's claim 43 calls for administering an acarbose formulation to a patient wherein the formulation does not include a lipase inhibitor. As defined in the specification and recited in the claims, an acarbose formulation is a mixture of acarbose and a sustained release matrix. (Ex. 1, pg. 1, lns. 18-20). Rosner, on the other hand, discloses administering acarbose with a meal of carbohydrates containing food. (Ex. 3, Col. 1, Ins. 16-18). Rosner does not describe each and every element as set forth in claim 43 because Rosner does not disclose administering a mixture of acarbose and a sustained release matrix. Since Rosner fails to recite each and every element of the claim, Rosner does not anticipate claim 43 under 35 U.S.C. § 102.

B. Claims 15-27 are Novel and the Rejection Under 35 U.S.C. § 102(e) Is Improper (Arguments Under 37 C.F.R. 1.192(c)(8)(iii))

The Examiner rejected claims 15-27 under 35 U.S.C. § 102(e) as being anticipated by Patel, U.S. Patent No. 6,309,663 (hereafter "Patel"). The Examiner contended that Patel

discloses a composition comprising surfactants and a hydrophilic therapeutic agent, such as acarbose (Ex. 6, pg. 3, ¶ 3).

1. The Amended Claims Cast in "Consisting Essentially of" Format are not Anticipated by Patel.

Applicant's amended claim 15 calls for a composition consisting essentially of acarbose and a sustained release matrix to form a mixture. As defined in the specification and recited in the claims, the sustained release matrix causes constant release of the acarbose over a period of time (Ex. 1, pg. 2, lns. 14-17). Patel does not anticipate claims 15-27 because Patel does not disclose a combination of acarbose and a sustained release matrix, which necessarily causes constant release of acarbose in a mixture.

Applicant has amended the claims to recite a composition consisting essentially of acarbose and sustained release matrix. "By using the term 'consisting essentially of' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic novel properties of the invention. A 'consisting essentially of' claim occupies the middle ground between closed claims that are written in a consisting of format and fully opened claims that are drafted in a comprising format." *PPG Industries v. Guardian Industries, Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) (citing *In re Herz*, 537 F.2d 549 (CCPA 1976)).

In *BASF Corp. v. Eastman Chemical Co.*, claim 6 of BASF's patent claimed a process for the catalytic rearrangement of EB to DHF which "consists essentially of the rearrangement being catalyzed by a system which contains components A and C from 60° to 200° C where A is an onium halide, which is substantially soluble in the reaction medium and C is a Lewis acid or elemental iodine with the provisio that at least one of the components A or C is an iodine." 56

U.S.P.Q.2d 1396, 1403 (D. Del. 1998). The court concluded that the phrase "consists essentially of" excludes the addition of any component B, a solublizer, because one of the basic and novel characteristics of claim 6 is that component A is intrinsically soluble. *Id.* at 1404-05. Because it is intrinsically soluble, the court found that component B was unnecessary for solubility and the addition of component B, a solublizer, and would alter this inherent trait. *Id.*

In another case, a claim directed to electrically insulating glass "consisting essentially of" nine ingredients but not including sulfur or carbon was not anticipated by a reference disclosing an amber-colored glass with no electrical insulating properties containing sulfur and carbon. *In re De Lajarte*, 337 F.2d 870, 873-74 (C.C.P.A. 1964). The court found that in showing that the claimed glass had the basic and novel properties of electrical insulation not possessed by the prior art, the Applicant met the burden of showing that the different composition could cause differences in the properties of the glass.

In light of the amendments, the claims call for a composition of acarbose and a sustained release matrix and any other component which does not alter the basic and novel characteristics of the composition. However, Patel teaches that hydrophilic therapeutic agents inherently experience multiple barriers to absorption. (Ex. 4, Col. 1, ln. 13-31). In order to overcome these inherent difficulties, Patel discloses a composition which includes an "absorption-enhancing agent" along with the particular hydrophilic therapeutic agent. As disclosed by Patel, the absorption-enhancing agent comprises at least two surfactants. (Ex. 4, Col. 4, lns. 1-13). Indeed, the Office concedes that Patel discloses a composition comprising at least two surfactants and a hydrophilic therapeutic agent, such as acarbose. (Ex. 6, pg. 3, ¶ 3). Patel further describes the

effects of the absorption enhancing combination of surfactants as "surprising" (Ex. 4, Col. 3, ln. 57) and "unexpected" (Ex. 4, Col. 4, ln. 57).

The Examiner states that "the presence of two surfactants would not necessarily enhance the 'rate, extent and/or consistency of bioabsorption' of a composition." (Ex. 2, pg. 3, ¶ 8). This position is untenable and misstates the teachings of the Patel reference. As indicated above, Patel expressly states that the two surfactants "enhances the rate, extent and/or consistency of bioabsorption of the hydrophilic therapeutic agents." (Ex. 4, Col. 4, lns. 54-58).

Patel's composition contains additional components including at least two surfactants. Applicant's claims exclude such additional components because the introduction of at least two surfactants would "materially affect the basic and novel characteristics" of the claimed invention, therefore Patel does not anticipate the instant claims. MPEP § 2111.03; *In re Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976) (emphasis in original). Applicant's composition results in the constant and controlled release of acarbose for absorption in the small intestine. Exactly as observed in the *BASF* court, because the present claims overcome the barriers to absorption without component B, at least two surfactants, the addition of component B, at least two surfactants, would alter an inherent trait. As such, claims 15-27 are not anticipated by Patel under 35 U.S.C. § 102(e).

2. Patel does not Disclose a Sustained Release Matrix.

The Examiner also asserted that "the Patel patent at column 39, line 31, clearly use [sic] the term 'sustained release' to described [sic] a component of their composition, which anticipates the 'sustained release matrix' of the instant claims." (Ex. 2, pg. 3, ¶ 8). Applicant

respectfully submits that the mere appearance of the term "sustained release" in Patel does not anticipate the "sustained release matrix" as recited in the instant claims.

Patel states that "coated compositions of the present invention allow...administration through...sustained release." (Ex. 4, Col. 39, lns. 26-31.) Thus, the "sustained release" as taught by Patel is a coating. *Id.* Patel further discloses that the coating of the combination of two surfactants and a therapeutic agent is an "enteric coating." (Ex. 4, Col. 38, lns. 37-43). This enteric coating is broadly defined as relating to "a mixture of pharmaceutically acceptable excipients which is applied, combined with, mixed with or otherwise added to the hydrophilic therapeutic agent." (Ex. 4, Col. 38, lns. 53-57). However, this enteric coating is not sustained release matrix, which alters the rate and extent of release, but rather an excipient altering the location of the release of the agent. As Patel states, the enteric coating causes release of the therapeutic agent in the lower gastrointestinal tract. (Ex. 4, Col. 38, lns. 36-43). To achieve this release profile, Patel teaches that the enteric coating is pH-dependent, whereby the coating does not dissolve in fluids at pH below about 5, but does dissolve in fluids at pH above about 5. (Ex. 4, Col. 39, lns. 37-40).

Moreover, the composition disclosed by Patel necessarily involves an uneven, uncontrolled release of the therapeutic agent. As the enteric coating of Patel dissolves, the composition is released, or essentially leaks out of the coating, at an uneven, uncontrolled rate. This discontinuous dissolution causes spikes in the therapeutic concentration of the active ingredient in the patient.

In contrast, as defined in the specification, the sustained release matrix as disclosed by Applicant causes constant, steady release of acarbose over a predetermined period of time. (Ex.

1, pg. 2, lns. 14-17). As embodied in claim 15, the composition provides a constant, controlled release of the formulation. Additionally, Applicant's sustained release matrix is pH-independent and the sustained release matrix is mixed with acarbose.

The Examiner alleged that "the features upon which applicant relies (i.e., location of the release of the agent, pH-independence, the acarbose and sustained release matrix being dry mixed) are not recited in the rejected claims" and therefore the limitations are not read into the claims. (Ex. 2, pg. 3, ¶ 8). However, these features, specifically the location of the release of the agent and the pH-independence of the composition, are properties of the exemplary composition disclosed, that is, acarbose and a sustained release matrix, and are included within the claims.

The sustained release matrix as recited in the claims is a pH independent matrix, which provides constant, controlled release of the formulation. Patel does not fairly disclose a sustained release matrix exhibiting the properties identified in the Applicant's sustained release matrix. Rather, Patel discloses that the "sustained release" is a pH dependent coating, which inherently causes an uneven and uncontrolled release in the lower gastrointestinal tract.

Patel's composition of at least two surfactants and a therapeutic agent, such as acarbose, does not include a sustained release matrix that causes constant release of the composition. Patel does not fairly disclose or suggest the sustained release matrix as claimed by Applicant, nor does Patel teach or suggest that acarbose be "mixed with" a sustained release matrix. Furthermore, Applicant's composition is limited to the active ingredient, acarbose, and a sustained release matrix. In contrast, Patel's composition contains a therapeutic agent and at least two surfactants. As Patel discloses, the additional at least two surfactants materially alter the characteristics of the composition by causing increased absorption. (Ex. 4, Col. 4, lns. 50-59). As such, it is

respectfully submitted that claims are not anticipated by Patel under 35 U.S.C. § 102(e) and the rejection has been overcome.

C. Claims 15-27 are Novel and the Rejection Under 35 U.S.C. § 102(b) Is Improper (Arguments Under 37 C.F.R. 1.192(c)(8)(iii))

The Examiner also rejected claims 15-27 as being anticipated under 35 U.S.C. § 102(b), by Bremer et al., U.S. Patent No. 5,643,874. The Examiner stated that Bremer discloses a composition of glucosidase and/or amylase inhibitors in combination with a lipase inhibitor in the treatment of obesity. (Ex. 6, pg. 4, ¶ 4). The Examiner reasoned that the claims as amended do not exclude the presence of the lipase inhibitor because "there is no indication in the Bremer et al patent that the presence of the lipase inhibitor in the composition of the Bremer et al patent alters the chemical formula of the acarbose and the hydroxypropylmethylcellulose of the Bremer et al patent." (Ex. 2, pg. 4, ¶ 10). The Examiner further asserted that because Applicant's have not claimed acarbose alone to stimulate weight loss, Bremer's disclosure does not teach away from Applicant's method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient. (Ex. 7, pg. 4, ¶ 12, pg. 6, ¶ 14).

As amended, Applicant has claimed a composition consisting essentially of acarbose and a sustained release matrix. Again, the language set forth in the amended claims excludes the presence of other ingredients that would change the novel and basic characteristics of the claimed composition. *See PPG Industries*, 156 F.3d at 1354. A lipase inhibitor is necessarily excluded because the addition of a lipase inhibitor to the claimed composition would materially alter the novel and basic characteristics of the claimed composition. As Bremer teaches, a lipase inhibitor causes inhibition of lipase. (Ex. 5, Col. 4, lns. 19-23). Acarbose does not cause any inhibition of lipase. By adding a lipase inhibitor to the composition of acarbose and a sustained

release matrix, the claimed composition would be materially altered because it would then cause the inhibition of lipase, a property not exhibited by Applicant's composition. When determining whether a particular ingredient is excluded by use of the transition "consisting essentially of," the basic and novel characteristics of the claimed composition are relevant, not merely the chemical formula of the claimed composition. Arguably, the chemical formula of the claimed composition would change with the presence of the other ingredient, since the claimed composition would now include the sustained release matrix, acarbose *and a lipase inhibitor.* However, the quintessential inquiry remains whether the presence of the other ingredient changes the "novel and basic characteristics of Applicant's claimed composition." *See PPG Industries*, 156 F.3d at 1354. Bremer clearly states that the lipase inhibitor causes inhibition of lipase, which adds a new activity and therefore changes the basic and novel characteristics of the claimed composition, namely acarbose and a sustained release matrix.

Furthermore, Bremer states that glucosidase and/or amylase inhibitors, *used in monotherapy* in combination with a reduction diet bring about "practically no weight loss," but that in combination with a lipase inhibitor does stimulate weight loss. (Ex. 5, Col. 4, lns 23-26). Applicant's composition, which lacks a lipase inhibitor, stimulates weight loss. (Ex. 1, Figure 1). Therefore, adding the additional component of a lipase inhibitor would alter this trait. Furthermore, Bremer clearly indicates that the presence of a lipase inhibitor in Bremer's composition alters the basic and novel characteristics of Bremer's composition. (Ex. 5, Col. 4, lns. 23-26). Since Bremer's composition includes a lipase inhibitor to effect weight loss, it does not anticipate the instant claims.

Moreover, Bremer does not disclose a composition consisting essentially of acarbose and sustained release matrix. As the specification discloses, the sustained release matrix, which is uniformly mixed with acarbose, causes a constant, controlled release of the composition over a predetermined period of time and such release occurs in the lower gastrointestinal tract. (Ex. 1, pg. 2, lns. 14-17). In contrast, the composition of Bremer only causes release and increased residence time in the stomach. (Ex. 5, Col 6, Ex. D). As discussed by Bremer, Bremer's formulation of Example D resulted in *release and increased residence time in the stomach,* not controlled, constant release of the formulation in the lower gastrointestinal tract as exhibited by Applicant's composition.

Applicant submits Bremer does not teach a composition consisting essentially of acarbose and a sustained release matrix. Applicant's disclosure states that a composition of acarbose and a sustained release matrix, in and of itself, will result in the stimulation of weight loss in a subject. Bremer clearly teaches away administering a composition of acarbose and no other active ingredients for stimulating weight loss. (Ex. 5, Col. 4, lns. 23-26). Based on Bremer's disclosure, one of ordinary skill in the art would not expect that administering a composition consisting essentially of acarbose and a sustained release matrix would stimulate weight loss. Thus, because Bremer includes additional active ingredients that change the novel and basic characteristics of claims 15-27 and fails to disclose the sustained release matrix, it does not anticipate under 35 U.S.C. § 102(b).

IX. CONCLUSION

It is respectfully submitted that claims 15-27 and 43 are allowable and the Examiner is urged to pass the application to allowance at an early date.

Respectfully submitted,

Dated: 15 OCT 2003

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Appendix A

15. (Previously Amended) A chemical composition used to stimulate weight loss in a patient, consisting essentially of:

acarbose; and

a sustained release matrix, wherein said acarbose and sustained release matrix are combined to form a mixture.

16. (Original) The composition of claim 15, wherein said acarbose is about 20% to about 40% by weight of said composition.

17. (Original) The composition of claim 15, wherein said acarbose is present in an amount of about 25mg to about 300mg.

18. (Previously Amended) The composition of claim 15, further consisting essentially of a filler.

19. (Previously Amended) The composition of claim 18, further consisting essentially of a glidant.

20. (Previously Amended) The composition of claim 19, further consisting essentially of a lubricant.

21. (Original) The composition of claim 19, wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

22. (Original) The composition of claim 20, wherein said lubricant is selected from the group consisting of sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates.

23. (Original) The composition of claim 20, wherein said lubricant is selected from the group consisting of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

24. (Original) The composition of claim 15, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

25. (Original) The composition of claim 15, wherein said composition is covered with a coating.

26. (Original) The composition of claim 25, wherein said coating is a cellulose ether-based coating.

27. (Original) The composition of claim 25, wherein said coating is a cellulose ether-based coating in combination with ethyl cellulose.

43. (Previously Added) A method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient, wherein such formulation does not include a lipase inhibitor.

Appendix A

15. (Previously Amended) A chemical composition used to stimulate weight loss in a patient, consisting essentially of:

acarbose; and

a sustained release matrix, wherein said acarbose and sustained release matrix are combined to form a mixture.

16. (Original) The composition of claim 15, wherein said acarbose is about 20% to about 40% by weight of said composition.

17. (Original) The composition of claim 15, wherein said acarbose is present in an amount of about 25mg to about 300mg.

18. (Previously Amended) The composition of claim 15, further consisting essentially of a filler.

19. (Previously Amended) The composition of claim 18, further consisting essentially of a glidant.

20. (Previously Amended) The composition of claim 19, further consisting essentially of a lubricant.

21. (Original) The composition of claim 19, wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

22. (Original) The composition of claim 20, wherein said lubricant is selected from the group consisting of sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates.

23. (Original) The composition of claim 20, wherein said lubricant is selected from the group consisting of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

24. (Original) The composition of claim 15, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

25. (Original) The composition of claim 15, wherein said composition is covered with a coating.

26. (Original) The composition of claim 25, wherein said coating is a cellulose ether-based coating.

27. (Original) The composition of claim 25, wherein said coating is a cellulose ether-based coating in combination with ethyl cellulose.

43. (Previously Added) A method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient, wherein such formulation does not include a lipase inhibitor.

METHOD AND COMPOSITION FOR CONTROLLED RELEASE ACARBOSE FORMULATIONS

BACKGROUND OF THE INVENTION

Acarbose is an inhibitor of the saccharase enzyme complex of the human small intestine and is used in medicine for the treatment of diabetes. Acarbose is chemically O-4,6-didesoxy-4-[(1S,4R,5S,5S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexan-1-yl amino]-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl((1→4)-D-glucopyranose. The active compound is obtained by fermentation.

U.S. Pat. No.4,904,769 to Rauenbusch discloses purified acarbose and a method for preparing same using column chromatography.

U.S. Pat. No. 4,767,850 to Lange et al. discloses the purification of acarbose by contacting an acarbose-containing solution with a polymeric cation exchanger.

U.S. Pat. No. 6,130,072 to Beunink et al. relates to a fermentative process for the preparation of acarbose.

Acarbose has been known for some time as an effective agent in the treatment of diabetes mellitus. It is marketed as an orally administered drug under the name Precose® and Glucobay®. Both Precose® and Glucobay® are simply coated with a delayed release coating. Precose® is available in 50 mg and 100 mg round tablets and is currently marketed in the United States by Bayer Corporation (Pharmaceutical Divisions, 400 Morgan Lane, West Haven, CT 06516).

SUMMARY OF THE INVENTION

The administration of acarbose alone has been shown to be useful in the treatment of diabetes. Although the initial studies conducted herein were conducted with a delayed release formulation that allowed partial sustained release administered to stimulate sustained release, all indicators from the present invention suggest the formulation of acarbose in a sustained release formulation would have heretofore unexpected benefits. In a sustained release formulation, the ingredient(s) would be a shaped dosage unit having a sustained and regular release of acarbose throughout the small intestine where carbohydrates as a simple sugar are absorbed.

The term "subject" as used herein means any mammal, including humans. The methods described herein contemplate prophylactic use as well as curative use in therapy for an existing condition.

In one embodiment of the present invention there is provided a method for providing sustained release administration of acarbose or a biological equivalent of thereof. The method allows a relatively constant release of acarbose over a pre-determined amount of time. Importantly, a slow release acarbose formulation provides substantially constant release of acarbose over a pre-determined period of time, thereby ameliorating a supply-demand mismatch involved with the current delayed release administration.

The method of producing the sustained release acarbose formulation, involves the steps of mixing acarbose with a sustained release matrix and compressing the resulting mixture to form tablets. The acarbose comprises about 20%-40% of the weight of the tablet, and ranges from an amount of 25 mg to 300 mg per tablet. Acarbose, a sustained release polymer such as hydroxypropylmethylcellulose (HPMC), and a filler are mixed together. The sustained release acarbose tablet is coated with a glidant, which is selected from the group consisting of colloidal silica, precipitated silica, and mixtures thereof. The sustained release matrix of the tablet is HPMC. The method of producing the sustained release acarbose formulation may also involve coating the tablet with ethyl cellulose.

In another embodiment of the present invention there is provided a composition comprised of acarbose and a sustained release polymeric matrix. Said acarbose may be present in the composition in the amount of 25 mg to 300 mg. Said acarbose in the composition is about 20% to 40% by weight of such composition.

In yet another embodiment of the present invention there is provided a method of treating a patient to stimulate weight loss, such method comprised of administering an acarbose formulation to the patient. The acarbose formulation may be mixed with a delayed release matrix, or alternatively may be mixed with a sustained release matrix.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating the mean weight change of patients administered delayed release acarbose in accordance with the present invention.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Sustained release products are widely recognized in the art and are of extreme importance in the pharmaceutical field. Through the use of such products, orally and rectally administered medications can be delivered continuously at a substantially uniform rate over a prolonged period of time so as to provide a stable, predetermined concentration of a drug in the small intestine, without requiring close monitoring and frequent re-administration.

Sustained release is achieved by a variety of methods. Two common methods are: 1) providing a sustained release coating upon tablets or microspheres wherein slow release of the active ingredient occurs via either gradual permeation through or gradual breakdown of this coating; or 2) providing a sustained release matrix, such as a fat, a wax, or a polymeric material intermixed with the active ingredient in the tablet itself. These are described for example in "Sustained Action Dosage Forms" *The Theory and Practice of Industrial Pharmacy*, Manford Robinson ch. 14 (L. Lachman et al., eds., 2d ed., 1976) which is incorporated herein by reference

thereto.

Sustained release matrix formulations are typically prepared by methods involving pre-granulating the active ingredient together with the matrix material via a wet granulation, solvent granulation, shear-melt or roto-melt granulation, or a wet pre-adsorption technique. In these techniques, a liquid phase is used in order to uniformly mix and/or closely contact the ingredients together so as to provide an evenly distributed matrix in intimate association with the active ingredient. These formation processes help prevent creation of interspersed quick-release zones which would result in discontinuous dissolution of the tablet and thus cause bioconcentration spikes of active ingredient in the patient. They frequently also result in tablets of a relatively higher density than the dry mixed ones, thus allowing the use of tablets, for a given dose, that are smaller than those made by dry mixing for the same intended release rate.

U.S. Pat. No. 4,259,314 to Lowey employs a mixture of cellulose ethers--hydroxypropylmethylcellulose ("HPMC") and hydroxypropyl cellulose--to form a sustained release matrix in which the cellulose ether mixture has a weighted average viscosity rating of 250-4500

U.S. Pat. No. 5,451,409 to Rencher et al. discloses a dry mixed tablet in which a mixture of hydroxypropyl cellulose and hydroxyethyl cellulose forms the sustained release matrix; 0.5-10% HPMC is also added as a binder.

U.S. Pat. No. 4,369,172; U.S. Pat. No. 4,389,393, & U.S. Pat. No. 4,983,396 to Forest discuss the use of HPMC in a variety of formulations.

Acarbose is an oral alpha-glucoside inhibitor approved for use in the management of non-insulin-dependent diabetes mellitus (NIDDM). Acarbose is complex oligosaccharide that delays the digestion of ingested carbohydrates. It is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. It has not been proven that metabolites have inhibitory activity on oligosaccharide digestion.

It is proposed that constant levels of acarbose parent compound throughout the gastrointestinal tract will produce constant inhibitory activity against the digestion of oligosaccharides, thus inhibiting the production of simple sugars. If the utilization of carbohydrates is inhibited, body fat will be used for energy, thus producing weight reduction.

Previous human experience with acarbose has demonstrated a favorable safety profile. Acarbose alone has not been shown to cause hypoglycemia, even when administered to patients in a fasted state. Gastrointestinal symptoms, namely flatulence, diarrhea and abdominal discomfort constitute the most common adverse events experienced by patients taking acarbose. These gastrointestinal symptoms, which have been shown to abate with time, are expected due to the mechanism of action of acarbose.

Humans can utilize only simple sugars. Reduction of complex sugars to simple sugars is a function of the membrane-bound intestinal alpha glucoside hydrolase. This action is inhibited by acarbose. For an agent with this mechanism, if action is to be useful in weight control, a method of keeping the agent in contact with the enteric mucosa over a 24-hour period would be desirable.

The present invention proposes a direct correlation between sustained release acarbose and weight loss. Therapeutic agent(s) may be incorporated in a pill or tablet form or deposited in or coated on the body of a sustained release device (e.g. in a polymeric matrix). The sustained release formulation is preferably comprised of acarbose and/or equivalents thereto. The sustained release formulation may be used with simultaneous or consecutive administration of other active agents. By appropriate choice of the material for the sustained release formulation, a physiologically active amount of acarbose and/or therapeutic mixture may be maintained for an extended period of time (e.g. 4-10 hours) depending on the form of administration and the acceptability of the form. The amount of acarbose or therapeutic mixture has been and will be determined empirically in accordance with known techniques using animal and human models.

Compositions of the present invention may include agents such as a stabilizing compound, which may be administered in any sterile, bio-compatible pharmaceutical carrier,

including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs or hormones. Pharmaceutically-acceptable carriers may also be comprised of excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA) hereby incorporated herein by reference in its entirety. The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.

After the controlled release compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

The exact dosage of the present invention will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect with tolerable side effects. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy.

The theory and mechanism presented herein are provided solely for the elucidation of the present invention and in no way are meant to limit the scope of the claims.

A sustained release formulation of acarbose (or a biological equivalent thereof) is to be incorporated in a tablet, capsule, or other administration route to achieve the benefits of the present invention. Acarbose in a controlled release formulation in and of itself is an improvement over the state of the art in that it supplies a relatively constant amount of acarbose throughout the bowel. An apparent supply-demand mismatch of acarbose in vivo heightens the need for a slow or controlled acarbose formulation.

The preferred embodiment of the present invention comprises extended-release tablets of an active ingredient which include a sustained release HPMC or ethylcellulose matrix. In a preferred embodiment of the present invention, a combination comprising at least one active ingredient together with hydroxypropylmethylcellulose (HPMC) is mixed and is directly compressed to form tablets. Preferably, the composition is prepared by dry mixing the ingredients. Preferably, one of the active ingredients is acarbose or a pharmacologically acceptable salt thereof. In a preferred embodiment, the amount of active ingredient used is that which is sufficient to produce tablets, each comprising in the range of about 10mg to 300mg active ingredient, even more preferably about 100mg to 250mg active ingredient, even more preferably about 150mg to 200mg active ingredient. A preferred HPMC is Methocel® K100M (produced by The Dow Chemical Co. of Midland, Mich.). Preferably about 20-40% HPMC is used, more preferably about 25-30% and most preferably about 28-29% HPMC.

Glidants, fillers, and other excipients that may be used in the preferred embodiments include those described, e.g., in Handbook of Pharmaceutical Excipients (J. C. Boylan et al., eds., 1986) and in H. A. Lieberman et al., Pharmaceutical Dosage Forms: Tablets (2d ed. 1990). Excipients generally may include: binders and adhesives; disintegrants, and adsorbents; glidants and lubricants; fillers and diluents; and colorants, sweeteners, and flavoring agents. Preferred fillers include calcium salts and simple sugars, for example, calcium phosphates, calcium sulfates, lactose, and mixtures thereof. More preferred fillers include dicalcium phosphate, tribasic calcium phosphate, directly compressible calcium sulfate, anhydrous lactose, flowable lactose (e.g., Fast Flo® lactose produced by Foremost Farms USA of Baraboo, Wis.), and mixtures thereof. Most preferred is dicalcium phosphate (Ca_2HPO). Preferably, about 20-40% by weight filler, based on the final weight of the tablets, is employed. However, where the filler consists of one or more sugars alone, preferably about 20-30% of filler is used.

Preferred glidants include colloidal silica and precipitated silica. A preferred colloidal silica is Cab-o-Sil® produced by the Cabot Corp. of Boston, Mass.; a preferred precipitated silica is Syloid® produced by W.R. Grace Co. of New York, N.Y. Preferably, about 0.2-2% by weight of glidant, based on the final weight of the tablets, is employed. Where

colloidal silica alone is used, the tablets will preferably comprise about 0.2-0.8% by weight glidant, more preferably about 0.25-0.75%. Preferred lubricants include sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates, alone or in combination with stearic acid. More preferred lubricants include magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof, alone or in combination with stearic acid. Preferably about 0.2-2%, by final weight of the tablets, of lubricant is used, more preferably about 0.25-1.25%. For example, where magnesium stearate is the sole lubricant, the tablets preferably comprise about 0.3-0.5% lubricant; where a magnesium stearate-stearic acid mixture is used as the lubricant, about 0.25% magnesium stearate may be mixed with as much as about 1% stearic acid.

In the preferred embodiment mixing procedure, the active ingredient, e.g., acarbose, sustained release polymer (e.g. HPMC, ethyl cellulose, Kollidon), and the filler, e.g., dicalcium phosphate dihydrate, are passed through a screen into a clean and dry blender, preferably in the order indicated. After mixing for 5 minutes, to the above mixture are added glidants, e.g. colloidal silicate, and this is then passed through a fine mesh screen and into a clean and dry blender. They are mixed for 5-20 minutes, following which a lubricant, e.g., magnesium stearate is screened into the blender and mixed in for an additional 5-15 minutes.

After the foregoing combination has been produced with thorough mixing, it is directly compressed to form tablets, i.e. any solid form, e.g., caplets. These are then coated with a pharmaceutically acceptable coating. Preferred coatings include cellulose ether-based coatings, such as HPMC-based coatings. A preferred coating is Opadry, produced by Colorcon, Inc. of West Point, Pa. Preferably about 0.54% by weight of coating is used (in terms of weight added to the uncoated tablet), more preferably about 1-2%. A wax, e.g., an edible wax such as carnauba wax, may also be applied as a second coating thereover.

Numerous advantages would appear to result from the ability to use acarbose in a sustained release dosage form. These include the use of smaller tablets which are more economical and are easy to administer. The sustained release drug forms of the present invention are expected to be stable and the release rate should not change over an extended storage period. The therapeutic compositions of the present invention, in most cases, will give a steady,

reproducible release of the active medicament. The acarbose compositions of the present invention can be formulated to act locally in the lumen or the bowel. The acarbose containing composition can be administered orally to transmit the active ingredients into the gastrointestinal tract. It is to be understood that the present invention is directed generally to an acarbose (or biological equivalent) either alone or in combination in a sustained release formulation and thus is applicable to compressed tablets intended to be swallowed in unit dosage form, and which upon ingestion according to a prescribed regimen give slow and regular release acarbose.

In making up tablets containing an orally administrable active component such as one of the heretofore mentioned, the oral carrier material is thoroughly intermixed with the acarbose and other active ingredients which is also in powdered or granular form or in solution, and any other needed ingredients which are conventional in tablet making such as magnesium stearate, lactose, starch and, in general, binders, fillers, disintegrating agents and the like. The complete mixture, in an amount sufficient to make a uniform batch of tablets, e.g. 50,000, of which each contains an effective amount of active medicament, is then subjected to tableting in conventional tableting machines at compression pressures of 2000 to 16000 lbs/in^2 and, because of the use of the specific carrier material of this invention in the production of the tablets, a product is obtained which has the desired hardness, low level of friability and a predetermined prolonged action and a regular delayed release pattern so that the medicament is available over a period of 4 to 10 hours, depending on the precise tablet size, hardness and the particular carrier composition. In this way, it is possible to produce sustained or slow continuous release tablets in relatively simple and economical manner on a commercial scale as contrasted with the more elaborate and more complex materials and procedures heretofore employed or proposed.

The release pattern of active medicament from the carrier of the present invention can be controlled according to the particular medication and its intended therapeutic effect. For a tablet, the release pattern may be varied from about 15 minutes to 4 hours. For orally administered tablets, the rate of release may be 4-10 hours, or as desired. Predetermined release patterns of unusually reliable and constant characteristics can be secured.

The excipient used to control the release of the active ingredient can be a variety of excipients commonly used in control release formulation. The two most common control

release excipients are hydroxylproylmethylcellulose ("HPMC") and ethylcellulose . Preferably the tablets formed with these excipients are processed by direct compression, and even more preferably are coated with a control release film. The control release film slows the initial burst of active ingredient. The following illustrative examples are provided for a better understanding of the present invention and are non-limiting. Variations will be obvious to those skilled in the art.

This delivery of sustained-release acarbose to the small intestine will produce maximum inhibition of carbohydrate utilization, resulting in weight control. A study was designed to determine the efficacy and safety of delayed-release acarbose tablets, in conjunction with diet and exercise, as a potential weight-control agent in non-diabetic, healthy, obese patients over a period of 16 weeks. Laboratory data was obtained to monitor the changes in levels of serum cholesterol, triglycerides and lipoprotein. Over the 16-week period, patients in Group A received 50 mg. enteric-coated acarbose tablets. All patients received acarbose 25 mg. t.i.d. during a 2-week pretreatment acclimatization phase. All patients underwent a 4-week follow-up phase where they ingested placebo tablets.

Prior to inclusion in the study, relevant baseline information was obtained for all participants. Such baseline information included medical history, physical examination, height and weight, electrocardiogram within two weeks of study initiation, and laboratory analyses.

Fig. 1 illustrates the mean weight change over the course of 16 weeks in participants receiving a delayed release acarbose formulation and those patients receiving a placebo. As can be seen, those patients receiving the delayed release formulation sustained a weight loss greater than those receiving a placebo. More specifically, of the thirteen subjects that were given an acarbose delayed release formulation, eleven lost weight, with the average weight loss being 7.4 pounds. All indicators from this study would suggest a sustained release formulation would also have benefits such as those described in connection with delayed release formulations.

The invention now being fully described in detail, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without

departing from the spirit or scope of the appended claims. For example it may be beneficial to combine the HPMC with an alkali earth metal to slow the drug release from the tablet (e.g. sodium carbonate or any alkali metal salt of a carboxylic acid). Additionally, new controlled release excipients may be used, such as Rollidon®. Such variations are considered to be within the scope of the invention, which is intended to be limited only to the scope of the claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

Each of the above-referenced U.S. Patents and publications are incorporated in their entirety by reference thereto.

What is claimed is:

1. A method for producing an extended-release composition comprising mixing acarbose with a sustained release matrix to create said composition.

2. The method of claim 1, further comprising compressing said mixture to form a tablet.

3. The method of claim 2, wherein said acarbose comprises about 20% to about 40% by weight of the tablet.

4. The method of claim 2, wherein said acarbose is present in an amount sufficient to produce the tablet in a range from about 25 mg to about 300 mg of said acarbose.

5. The method of claim 1, wherein the mixing step further utilizes a filler.

6. The method of claim 5, wherein the mixing step further utilizes a glidant.

7. The method of claim 6, wherein the mixing step further utilizes a lubricant.

8. The method of claim 6, wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

9. The method of claim 7, wherein said lubricant is selected from the group consisting of sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates.

10. The method of claim 7, wherein said lubricant is selected from the group consisting of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

11. The method of claim 1, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

12. The method of claim 2, further comprising the step of covering said tablet with a coating.

13. The method of claim 12, wherein said coating is a cellulose ether-based coating.

14. The method of claim 12, wherein said coating is a cellulose ether-based coating in combination with ethyl cellulose.

15. A chemical composition comprising:
acarbose; and
a sustained release matrix.

16. The composition of claim 15, wherein said acarbose is about 20% to about 40% by weight of said composition.

17. The composition of claim 15, wherein said acarbose is present in an amount of about 25mg to about 300mg.

18. The composition of claim 15, further comprising a filler.

19. The composition of claim 18, further comprising a glidant.

20. The composition of claim 19, further comprising a lubricant.

21. The composition of claim 19, wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

22. The composition of claim 20, wherein said lubricant is selected from the group consisting of sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates.

23. The composition of claim 20, wherein said lubricant is selected from the group consisting of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

24. The composition of claim 15, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

25. The composition of claim 15, wherein said composition is covered with a coating.

26. The composition of claim 25, wherein said coating is a cellulose ether-based coating.

27. The composition of claim 25, wherein said coating is a cellulose ether-based coating in combination with ethyl cellulose.

28. A method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient.

29. The method of claim 28, wherein said acarbose formulation comprises acarbose; and
a delayed release matrix.

30. The method of claim 28, wherein said acarbose formulation comprises acarbose; and
a sustained release matrix.

31. The method of claim 30, wherein said acarbose is about 20% to about 40% by weight of said composition.

32. The method of claim 30, wherein said acarbose is present in an amount of about 25mg to about 300mg.

33. The method of claim 30, wherein said acarbose formulation further comprises a filler.

34. The method of claim 33, wherein said acarbose formulation further comprises a glidant.

35. The method of claim 34, wherein said acarbose formulation further comprises a lubricant.

36. The method of claim 34, wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

37. The method of claim 35, wherein said lubricant is selected from the group consisting of sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates.

38. The method of claim 35, wherein said lubricant is selected from the group consisting of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

39. The method of claim 30, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

40. The method of claim 30, wherein said acarbose formulation is covered with a coating.

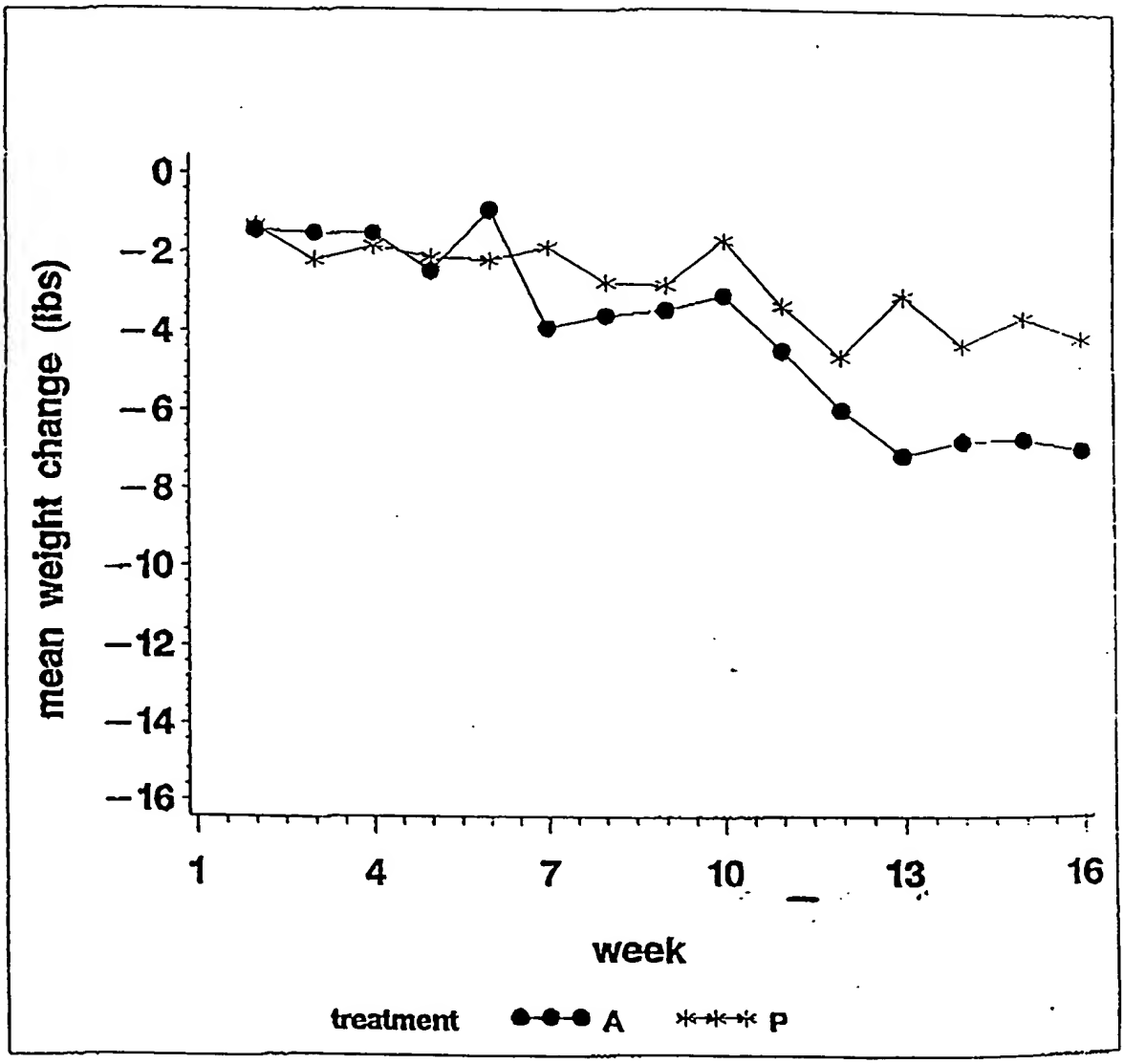
41. The method of claim 40, wherein said coating is a cellulose ether-based coating.

42. The method of claim 41, wherein said coating is a cellulose ether-based coating in combination with ethyl cellulose.

ABSTRACT

The present invention is directed towards a method and composition for controlled release acarbose formulations. The method and composition disclosed herein combine acarbose and a sustained release matrix. The administration of acarbose alone has been shown to be useful in the treatment of diabetes. Although the initial studies conducted herein were conducted with a delayed release formulation that allowed partial sustained release administered to stimulate sustained release, all indicators from the present invention suggest the formulation of acarbose in a sustained release formulation would have heretofore unexpected benefits. In a sustained release formulation, the ingredient(s) would be a shaped dosage unit having a sustained and regular release of acarbose throughout the small intestine where carbohydrates as a simple sugar are absorbed.

Figure 1.


mean weight change (lbs)
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PATENT & TRADEMARK OFFICE

EXAMINER
WHITE, EVERETT NMN

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,707	MORRISON, JAMES U.	
	Examiner	Art Unit	
	EVERETT WHITE	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-27 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-27 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed July 15, 2003 has been received, entered and carefully considered. The amendment affects the instant application accordingly:

(A) Claims 1-14 and 28-42 have been canceled;
(B) Claims 15 and 18-20 have been amended.
(C) Comments regarding the Art Rejections have been provided drawn to:
  (a) 102(b) and (e) rejection, which has been maintained for the reasons of record;
  (b) 103(a) rejection, which has been withdrawn.

2. Claims 15-27 and 43 are pending in the case.

3. The text of those sections of title 35, U. S. Code not included in this action can be found in a prior Office action.

Final Office Action Withdrawn

4. The finality of the Office Action mailed March 7, 2003 has been withdrawn for the reasons disclosed below.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 43 is rejected under 35 U.S.C. 102(a) as being anticipated by Rosner (US Patent No. 6,387,361, already of record).

Applicants claim a method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient, wherein such formulation does not include a lipase inhibitor.

The Rosner patent discloses a method of controlling weight in a human comprising administering to the human acarbose at meals with food containing carbohydrate, which anticipates the method of instant Claim 43.

6. Applicant's arguments with respect to Claim 43 have been considered but are moot in view of the new ground(s) of rejection.

7. Claims 15-27 stand rejected under 35 U.S.C. 102(e) as being anticipated by Patel et al (US Patent No. 6,309,663, already of record) for the reasons already of record in the previously filed Office Actions.

8. Applicant's arguments filed July 15, 2003 have been fully considered but they are not persuasive. Applicants amended the claims by changing the term "comprising" to -- consisting essentially of --. Applicants argue that the instant claims as amended exclude additional components of the Petel's composition that include at least two surfactants. Applicants argue that their composition, namely "the rate, extent and/or consistency of bioabsorption" of the composition would be unexpectedly enhanced in the presence of "at least two surfactants". This argument is not persuasive since the presence of two surfactants would not necesarrily enhance "the rate, extent and/or consistency of bioabsorption" of a composition. Applicants argue that the Patel patent does not disclose a sustained release matrix. This argument is not persuasive since the Patel patent at column 39, line 31, clearly use the term "sustained release" to described a component of their composition, which anticipates the "sustained release matrix" of the instant claims. In response to applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which applicant relies (i.e., location of the release of the agent, pH-independence, the acarbose and sustained release matrix being dry mixed) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly, the rejection of Claims 15-27 under 35 U.S.C. 102(e) as being anticipated by the Patel et al patent is maintained for the reasons of record.

9. Claims 15-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bremer et al (US Patent No. 5,643,874, already of record) for the reasons already of record in the previously filed Office Actions.

10. Applicant's arguments filed July 15, 2003 have been fully considered but they are not persuasive. Applicants argue against the rejection of Claims 15-27 over the Bremer et al patent on the grounds that the claims as amended (changing "comprising" to "consisting essentially of") excludes the presence of other ingredients that would change the novel and basic characteristics of the claimed composition. If Applicants are referring to the novel and basic characteristics of the claimed composition as the acarbose and sustained release matrix, then this argument is not persuasive since there is no indication in the Bremer et al patent that the presence of the lipase inhibitor in the composition of the Bremer et al patent alters the chemical formula of the acarbose and the hydroxypropylmethylcellulose of the Bremer et al patent. See instant Claim 24 wherein the sustained release matrix is hydroxypropylmethylcellulose. Applicants argue that the hydroxypropylmethylcellulose of the Bremer et al patent only causes release and increase residence time in the stomach. This argument is not persuasive. Applicants are reminded that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. It is further noted that the Bremer et al patent indicates that the composition thereof is used in the treatment of obesity, which further supports anticipation of the Bremer et al patent over the instant claims since the instant specification teaches the use of the instantly claimed composition to stimulate weight loss. Accordingly, the rejection of Claims 15-27 under 35 U.S.C. 102(b) as being anticipated by the Bremer et al patent is maintained for the reasons of record.

Summary

11. All the pending claims are rejected.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner's Telephone Number, Fax Number, and Other Information

For 24 hour access to patent application information 7 days per week, or for filing applications, please visit out website at **www.uspto.gov** and click on the button "Patent Electronic Business Center" for more information.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Everett White whose telephone number is (703) 308-4621. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reach on (703) 308-4624. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

E.White

James O. Wilson
Supervisory Primary Examiner
Technology Center 1600

Mail with Office Action

US006387361B1

(12) **United States Patent**
Rosner

(10) **Patent No.: US 6,387,361 B1**
(45) **Date of Patent: May 14, 2002**

(54) **USE FOR DRUG ACARBOSE PRECOSE FOR WEIGHT CONTROL PREVENTION OF WEIGHT GAIN FOR WEIGHT LOSS FOR TREATMENT AND PREVENTION OF OBESITY**

(76) Inventor: **Harvey Rosner**, 530F Grand St. Apt. 3F, New York, NY (US) 10002

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/364,992**

(22) Filed: **Aug. 2, 1999**

(51) **Int. Cl.**[7] **A61K 31/74**
(52) **U.S. Cl.** **424/78.01**; 435/18
(58) **Field of Search** 424/78.01; 435/18

(56) **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—James O. Wilson

(57) **ABSTRACT**

Control of weight gain has long been a problem for many people who if they lose weight by dieting often gain it back in a short period of time. Therefore, there has been much research to find a simple means to control weight in humans.

Acarbose, an oligosaccharide, is an oral alpha glucosidase inhibitor. The mechanism of action of acarbose results from a competitive inhibition of pancreatic amylase and membrane bound intestinal aplpha-glucoside hydrolase enzymes. Pancreatic alpha amylase hydrolizes complex starches in the lumen of the small intestine. The membrane bound intestinal alpha glucosidases hydrolyze oligo saccharides, trissaccharides and disaccharides to glucose and other monosaccharides in the brush boarder of the small intestines. It has no inhibitory effect against lactase and would therefore not be expected to induce the symptoms of lactose intolerance. The weight gain or loss for an individual is essentially the difference between the calories absorbed and the calories burned.

4 Claims, No Drawings

USE FOR DRUG ACARBOSE PRECOSE FOR WEIGHT CONTROL PREVENTION OF WEIGHT GAIN FOR WEIGHT LOSS FOR TREATMENT AND PREVENTION OF OBESITY

OBJECTS OF THE INVENTION

It is an object of the invention to control weight in humans by ingesting acarbose with meals with food containing carbohydrates.

This and other objects and advantages will become obvious from the following detailed description.

THE INVENTION

The invention is directed to a method of controlling weight in human beings by ingesting acarbose at meals with food containing carbohydrates. Acarbose is known to be an oral -glucosidase inhibitor, which acts by a reversible inhibitor of membrane-bound intestinal -glucoside hydraslase enzymes. Membrane intestinal -glucosidases hydrolize oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine.

Weight gain or loss for an individual is essentially the difference between the amount of calories absorbed and the amount of calories burned. Acarbose apparently exerts it's effect by blocking the absorption of carbohydrates, which means a portion of the carbohydrates consumed at the meal are not absorbed by the body but are excreted by the body rather than absorbed due to the action of acarbose. Acarbose does not affect the digestion of proteins or fats. This lower absorption of carbohydrates results in less weight gain due to the lower consumption of calories.

To be effective, the diet must contain carbohydrates above the monosacchoride level and the use of acarbose for weight control is a major breakthrough in the field of weight control. Treatment with acarbose is a relatively safe method for weight control as the side effects of acarbose are minimal as can be seen from the 2000 physician's desk manual.

Acarbose has been used for the treatment of type II diabetes and is marketed under the mark Precose® by Bayer in tablet dose of 25, 50 and 100 mg. Acarbose is a prescription drug and the exact dosage for weight control will be determined by the attending physician as a result of the clinical response of the patient. I have determined from my studies that normally the dosage per meal is dependent upon the amount of carbohydrates in the meal. Acarbose can also be administered as a wafer or can be mixed with the food to reduce the carbohydrate absorption.

The method of weight control can be used to control weight gain, to provide weight loss and for the prevention or treatment of obesity depending upon the amount of carbohydrates consumed at the meals. For example, if a person overindulge during the holiday season, the consumption of acarbose at the meals will lower the amount of weight gained because at least a portion of the carbohydrates are excreted rather than absorbed.

Besides blocking absorption of carbohydrates, acarbose encourages bacterial fermentation in the digestive tract for more gas production, which gives the feeling of fullness, reducing the amount of food consumed at the meal. This results in a psychological deterrent to over eating.

Various modifications of the method of the invention may be made without departing from the spirit or scope thereof. It is to be understood that the invention is intended to be limited only as defined in the appended claims.

What I claim is:

1. A method of controlling weight in a human comprising administering to humans in need thereof with a meal of carbohydrate containing food an amount of acarbose sufficient to lower carbohydrate absorption.

2. The method of claim 1 wherein the human is obese.

3. The method of claim 1 wherein the amount of acarbose used results in a weight loss by the human.

4. The method of claim 1 wherein the amount of acarbose used results in reduced weight gain.

* * * * *

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For assistance: Any questions regarding the submission of amendments pursuant to the revised practice should be directed to Office of Patent Legal Administration (OPLA), Legal Advisors Elizabeth Dougherty (**Elizabeth.Dougherty@uspto.gov**), Gena Jones (**Eugenia.Jones@uspto.gov**) or Joe Narcavage (**Joseph.Narcavage@uspto.gov**). Alternately, you may send e-mail to "Patent Practice", the OPLA e-mail address that has been established for receiving queries and questions about patent practice and procedures or telephone OPLA at (703) 305-1616.

Nicholas P. Godici
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US006309663B1

(12) **United States Patent**
Patel et al.

(10) **Patent No.: US 6,309,663 B1**
(45) **Date of Patent: Oct. 30, 2001**

(54) **TRIGLYCERIDE-FREE COMPOSITIONS AND METHODS FOR ENHANCED ABSORPTION OF HYDROPHILIC THERAPEUTIC AGENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(52) **U.S. Cl.** **424/450**; 424/451; 424/455; 424/456; 424/463; 424/489; 424/499; 424/502; 424/435; 424/464; 514/937; 514/938; 514/939; 514/940; 514/941; 514/942; 514/943; 514/975

(58) **Field of Search** 424/450, 451, 424/455, 456, 463, 489, 499, 502, 435, 464; 514/937–943, 975

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(57) **ABSTRACT**

The present invention relates to pharmaceutical compositions, pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. Compositions and systems of the present invention include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the composition, or can be co-administered with the composition as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compositions and systems.

170 Claims, No Drawings

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TRIGLYCERIDE-FREE COMPOSITIONS AND METHODS FOR ENHANCED ABSORPTION OF HYDROPHILIC THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to drug, nutrient and diagnostic agent delivery systems, and in particular to pharmaceutical systems and methods for the improved delivery and enhanced absorption of hydrophilic therapeutic agents.

BACKGROUND

Hydrophilic therapeutic agents present difficult problems in formulation. While these therapeutic agents are readily soluble in water, and are easily dissolved in the gastrointestinal environment, simple dissolution is not sufficient to provide efficient bioabsorption of the therapeutic agent. Barriers to absorption are presented by the mucous layer, the intestinal epithelial cell membrane, and the junctional structure such as tight junctions between the epithelial cells. Due to the presence of the negatively charged mucosal layer, significant electrostatic binding or repulsion of charged molecules can be encountered. The epithelial cell membranes are composed of phospholipid bilayers in which proteins are embedded via the hydrophobic segments. These bilayers at the apical and/or basolateral cell surface represent very strong barriers for transport of hydrophilic substances, including peptides and proteins. Frequently, hydrophilic therapeutic agents are also subject to enzymatic attack and are degraded before they can be presented to the absorption site.

Some hydrophilic drugs such as acyclovir, foscarnet, tiludronate, pamidronate, alendronate, acarbose, cromolyn sodium, aminoglycoside and cephalosporin antibiotics are poorly absorbed from the gastro-intestinal tract, due to their low octanol-water partition coefficient, charge, and/or size.

Large water-soluble polymers, such as peptides, proteins, genetic material, vaccines and oligonucleotides, are not well absorbed from the intestine, primarily due to their low membrane permeability and enzymatic inactivation. The mammalian body possesses several efficient mechanisms to restrict the entry of macromolecules. These mechanisms include the presence of significant levels of enzymatic activity at various locations prior to entry into systemic circulation.

Thus, numerous barriers to absorption of hydrophilic therapeutic agents are present, and these barriers inhibit the effective absorption both of small hydrophilic therapeutic agents, such as conventional non-peptidic drugs, and of macromolecular hydrophilic therapeutic agents, such as proteins, peptides, vaccines and the like.

Much effort has been expended to develop methods of overcoming these absorption barriers. For example, the enzymatic barrier can be attacked by administering enzyme inhibitors to prevent or at least lessen the extent of presystemic degradation in the gastrointestinal tract (see, e.g., Bernkop-Schnurch, "The use of inhibitory agents to overcome the enzymatic barrier to perorally administered therapeutic peptides and proteins", *Journal of Controlled Release*, 52, 1–16 (1998)). Other efforts have focused on, for example, the use of absorption promoters to enhance epithelial permeability (e.g., LeCluyse and Sutton, "In vitro models for selection of development candidates. Permeability studies to define mechanisms of absorption enhancement", *Advanced Drug Delivery Reviews*, 23, 163–183 (1997)). However, the effectiveness of absorption

enhancers such as permeability enhancers or enzyme inhibitors depends upon the ability of a pharmaceutical carrier to effectively present the absorption enhancers and the hydrophilic therapeutic agent to the absorption site, and prior efforts have not provided carriers which can do so efficiently. Moreover, maintaining effective carrier concentrations at the epithelium is not easily controlled in vivo. Too little carrier, or carrier concentrations only briefly maintained, may be ineffective. Too much carrier, or carrier concentrations maintained for too long, may result in compromised safety.

Frequently, carrier compositions for hydrophilic therapeutic agents include or are based on triglycerides. For example, U.S. Pat. Nos. 5,444,041, 5,646,109 and 5,633,226 to Owen et al. are directed to water-in-oil ("w/o") microemulsions for delivering water-soluble biological actives, such as proteins or peptides. The water-in-oil microemulsions convert into oil-in-water ("o/w") emulsions upon ingestion. The active agent is initially stored in the internal water phase of the w/o microemulsion, and is released when the composition converts to an o/w emulsion upon mixing with bodily fluids. Other oil-based or oil-containing formulations are taught in, for example, U.S. Pat. No. 5,120,710 to Liedtke, U.S. Pat. No. 5,656,289 to Cho et al. These triglyceride-containing formulations, however, suffer form several disdavantages.

U.S. Pat. No. 5,206,219 to Desai, for example, teaches compositions having a particle size of 5 to 50 microns. Typically, emulsions formed from triglyceride-containing compositions contain colloidal oil particles which are relatively large, ranging from several hundred nanometers to several microns in diameter, in a broad particle size distribution. Since the particle sizes are on the order of or greater than the wavelength range of visible light, such emulsions, when prepared in an emulsion dosage form, are visibly "cloudy" or "milky" to the naked eye. Emulsions are thermodynamically unstable, and colloidal emulsion particles will spontaneously agglomerate, eventually leading to complete phase separation. The tendency to agglomerate and phase separate presents problems of storage and handling, and increases the likelihood that pharmaceutical emulsions initially properly prepared will be in a less optimal, less effective, and poorly-characterized state upon ultimate administration to a patient. Uncharacterized degradation is particularly disadvantageous, since increased particle size slows the rate of transport of the colloidal particle and digestion of the oil component, and hence the rate and extent of absorption of the therapeutic agent. These problems lead to poorly-characterized and potentially harmful changes in the effective dosage received by the patient, and/or the rate of drug uptake. Moreover, changes in colloidal emulsion particle size are also believed to render absorption more sensitive to and dependent upon conditions in the gastrointestinal tract, such as pH, enzyme activity, bile components, and stomach contents. Such uncertainty in the rate and extent of ultimate absorption of the therapeutic agent severely compromises the medical professional's ability to safely administer therapeutically effective dosages. In addition, when such compositions are administered parenterally, the presence of large particles can block blood capillaries, further compromising patient safety.

U.S. Pat. No. 5,626,869 to Nyqvist et al. discloses compositions that would likely produce discrete lipid particles of relatively large size in vivo. Such particles suffer from the disadvantages of large size and low diffusivity, and are unable to effectively present any absorption enhancing components to the site of absorption.

A further disadvantage of conventional triglyceride-containing compositions is the dependence of therapeutic

agent absorption on the rate and extent of lipolysis. Ultimately the triglyceride must be digested and the therapeutic agent must be released in order to be absorbed through the intestinal mucosa. The triglyceride carrier is emulsified by bile salts and hydrolyzed, primarily by pancreatic lipase. The rate and extent of lipolysis, however, are dependent upon several factors that are difficult to adequately control. For example, the amount and rate of bile salt secretion affect the lipolysis of the triglycerides, and the bile salt secretion can vary with stomach contents, with metabolic abnormalities, and with functional changes of the liver, bile ducts, gall bladder and intestine. Lipase availability in patients with decreased pancreatic secretory function, such as cystic fibrosis or chronic pancreatitis, may be undesirably low, resulting in a slow and incomplete triglyceride lipolysis. The activity of lipase is pH dependent, with deactivation occurring at about pH 3, so that the lipolysis rate will vary with stomach contents, and may be insufficient in patients with gastric acid hyper-secretion. Moreover, certain surfactants commonly used in the preparation of pharmaceutical emulsions, such as polyethoxylated castor oils, may themselves act as inhibitors of lipolysis.

Other carrier formulations avoid the use of triglycerides, but still suffer disadvantages. For example, U.S. Pat. No. 5,653,987 to Modi et al. is directed to pharmaceutical formulations for oral or nasal delivery of proteinaceous pharmaceutical agents using small amounts of particular surfactants and a protease inhibitor in an aqueous medium as absorption enhancers. However, in the gastrointestinal tract, where the volume of liquids is large and motility is great, polar drugs and the protease inhibitor are diluted even further upon administration, thus negating any potential benefits, since the composition is unable to deliver meaningful amounts of the absorption enhancers and pharmaceutical agents to the absorption site.

Thus, there is a need for pharmaceutical compositions that overcome the limitations of conventional formulations, to provide effective delivery of absorption enhancers and enhanced absorption of hydrophilic therapeutic agents.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide pharmaceutical systems capable of efficiently presenting hydrophilic therapeutic agents and absorption enhancing components to the absorption site.

It is another object of the present invention to provide pharmaceutical systems for delivery of a hydrophilic therapeutic agent that are not dependent upon lipolysis for bioabsorption.

It is another object of the present invention to provide pharmaceutical systems capable of increasing the rate and/or extent of bioabsorption of hydrophilic therapeutic agents.

In accordance with these and other objects and features, the present invention provides triglyceride-free pharmaceutical systems for enhanced bioabsorption of hydrophilic therapeutic agents. It has been surprisingly found that pharmaceutical compositions having absorption enhancing properties can be provided by using a combination of surfactants in amounts such that when the pharmaceutical composition is mixed with an aqueous diluent, an aqueous dispersion having a very small average particle size is formed. Such compositions can be co-administered with a hydrophilic therapeutic agent to increase the rate and/or extent of bioabsorption of the hydrophilic therapeutic agent, or can be provided with a hydrophilic therapeutic agent in the preconcentrate composition or in a diluent solution.

In one embodiment, the present invention relates to triglyceride-free pharmaceutical systems having a dosage form of an absorption enhancing composition comprising at least two surfactants, at least one of which is hydrophilic, and a hydrophilic therapeutic agent The surfactants are present in amounts such that the carrier forms an aqueous dispersion having a very small average particle size upon mixing with an aqueous diluent. The hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and suspended, in the absorption enhancing carrier. Alternatively, the hydrophilic therapeutic agent can be provided separately, for co-administration with the dosage form of the absorption enhancing composition.

In another embodiment, the present invention provides a triglyceride-free pharmaceutical system for enhanced absorption of a hydrophilic therapeutic agent, including a dosage form of an absorption enhancing composition, and a hydrophilic therapeutic agent, wherein the absorption enhancing composition has at least one hydrophilic surfactant and at least one hydrophobic surfactant. The surfactants are present in amounts such that the carrier forms an aqueous dispersion having a very small average particle size upon mixing with an aqueous diluent. The hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and suspended, in the dosage form of the absorption enhancing composition, or provided in a separate dosage form.

In another embodiment, the present invention provides a method of improving the bioabsorption of a hydrophilic therapeutic agent administered to a patient. The method includes the steps of providing a dosage form of an absorption enhancing composition, providing a hydrophilic therapeutic agent, and administering the dosage form of the absorption enhancing composition and the hydrophilic therapeutic agent to a patient. The method improves bioabsorption by improving the consistency of delivery of the hydrophilic therapeutic agent to the absorption site, and providing absorption enhancers at the absorption site.

These and other objects and features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention overcomes the problems described above characteristic of conventional formulations of hydrophilic therapeutic agents by providing unique pharmaceutical systems for enhanced absorption of hydrophilic therapeutic agents. The pharmaceutical systems include absorption-enhancing components which, when the compositions are mixed with an aqueous diluent either in vitro or in vivo, form aqueous dispersions having a very small particle size. The combination of absorption enhancing compounds at relatively high concentration, very small particle sizes upon dispersion, and the absence of triglycerides unexpectedly enhances the rate, extent and/or consistency of bioabsorption of hydrophilic therapeutic agents present in, or co-administered with, the absorption enhancing compositions.

The term "absorption enhancement" as used herein means an improvement in one or more of the rate of bioabsorption, the extent of bioabsorption, and the consistency of the rate and/or extent of bioabsorption. Without wishing to be bound by theory, it is believed that the absorption enhancement provided by the pharmaceutical systems of the present invention is a result of one or more of the following factors:

(1) effective presentation of an absorption enhancer to the site of enhancement;

(2) modulation of facilitated/active transport;

(3) transcellular permeability enhancement through favorable membrane perturbations;

(4) inhibition of efflux related transporters;

(5) inhibition of lumenal or cellular enzymatic inactivation;

(6) paracellular transport enhancement through loosening of tight junctions;

(7) induction of specific transporters to facilitate transport;

(8) altered biological binding characteristics;

(9) reduced degradation of the hydrophilic therapeutic agent;

(10) induction of transient water channels; and/or

(11) increased partitioning of the hydrophilic therapeutic agent by association with the absorption enhancer.

A. Pharmaceutical Compositions and Methods

In one embodiment, the present invention provides a triglyceride-free pharmaceutical system including an absorption enhancing composition. The absorption enhancing composition includes at least two surfactants, at least one of which is a hydrophilic surfactant. Preferably, the carrier includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. The surfactants are present in amounts such that upon dilution with an aqueous diluent, either in vitro or in vivo, the carrier forms an aqueous dispersion having a small average particle size. The hydrophilic and hydrophobic surfactants are believed to function as absorption enhancers, and the hydrophilic surfactant additionally assists the functionality of other absorption enhancing hydrophilic or hydrophobic surfactants.

1. Surfactants

The absorption enhancing composition includes at least two surfactants, at least one of which is a hydrophilic surfactant. Preferably, the composition includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties; i.e., a surfactant compound must be amphiphilic. An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units, depending upon the empirical method chosen to determine the HLB value (Schott, *J. Pharm. Sciences*, 79(1), 87–88 (1990)). Likewise, for certain polypropylene oxide containing block copolymers (PLURONIC® surfactants, BASF Corp.), the HLB values may not accurately reflect the true physical chemical nature of the compounds. Finally, commercial surfactant products are generally not pure compounds, but are complex mixtures of compounds, and the HLB value reported for a particular compound may more accurately be characteristic of the commercial product of which the compound is a major component. Different commercial products having the same primary surfactant component can, and typically do, have different HLB values. In addition, a certain amount of lot-to-lot variability is expected even for a single commercial surfactant product. Keeping these inherent difficulties in mind, and using HLB values as a guide, one skilled in the art can readily identify surfactants having suitable hydrophilicity or hydrophobicity for use in the present invention, as described herein.

The hydrophilic surfactant can be any hydrophilic surfactant suitable for use in pharmaceutical compositions. Such surfactants can be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are presently preferred. As discussed above, these non-ionic hydrophilic surfactants will generally have HLB values greater than about 10. Mixtures of hydrophilic surfactants are also within the scope of the invention.

Similarly, the hydrophobic surfactant can be any hydrophobic surfactant suitable for use in pharmaceutical compositions. In general, suitable hydrophobic surfactants will have an HLB value less than about 10. Mixtures of hydrophobic surfactants are also within the scope of the invention.

The choice of specific hydrophobic and hydrophilic surfactants should be made keeping in mind the particular hydrophilic therapeutic agent to be used in the composition, and the range of polarity appropriate for the chosen hydrophilic therapeutic agent, as discussed in more detail below. With these general principles in mind, a very broad range of surfactants is suitable for use in the present invention. Such surfactants can be grouped into the following general chemical classes detailed in the Tables herein. The HLB values given in the Tables below generally represent the HLB value as reported by the manufacturer of the corresponding commercial product. In cases where more than one commercial product is listed, the HLB value in the Tables is the value as reported for one of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable. It should be emphasized that the invention is not limited to the surfactants in the Tables, which show representative, but not exclusive, lists of available surfactants.

1.1. Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are especially useful. Among the surfactants of Table 1, preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 1.

TABLE 1

PEG-Fatty Acid Monoester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6
PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100, 200, 300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100, 200, 300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400–1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-1EX (Nikko), Coster K1 (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg ® 200 ML (PPG), Kessco ® PEG 200 ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9.3
PEG-4 oleate	Mapeg ® 200 MO (PPG), Kessco ® PEG 200 MO (Stepan),	8.3
PEG-4 stearate	Kessco ® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5
PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco ® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
PEG-6 laurate	Kessco ® PEG 300 ML (Stepan)	11.4
PEG-7 laurate	Lauridac 7 (Condea)	13
PEG-6 stearate	Kessco ® PEG 300 MS (Stepan)	9.7
PEG-8 laurate	Mapeg ® 400 ML (PPG), LIPOPEG 4DL (Lipo Chem.)	13
PEG-8 oleate	Mapeg ® 400 MO (PPG), Emulgante A8 (Condea); Kessco PEG 400 MO (Stepan)	12
PEG-8 stearate	Mapeg ® 400 MS (PPG), Myrj 45	12
PEG-9 oleate	Emulgante A9 (Condea)	>10
PEG-9 stearate	Cremophor 59 (BASF)	>10
PEG-10 laurate	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
PEG-10 oleate	Nikkol MYO-10 (Nikko)	11
PEG-10 stearate	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
PEG-12 laurate	Kessco ® PEG 600 ML (Stepan)	15
PEG-12 oleate	Kessco ® PEG 600 MO (Stepan)	14
PEG-12 ricinoleate	(CAS #9004-97-1)	>10
PEG-12 stearate	Mapeg ® 600 MS (PPG), Kessco ® PEG 600 MS (Stepan)	14
PEG-15 stearate	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
PEG-15 oleate	Nikkol TMGO-15 (Nikko)	15
PEG-20 laurate	Kessco ® PEG 1000 ML (Stepan)	17
PEG-20 oleate	Kessco ® PEG 1000 MO (Stepan)	15
PEG-20 stearate	Mapeg ® 1000 MS (PPG), Kessco ® PEG 1000 MS (Stepan), Myrj 49	16
PEG-25 stearate	Nikkol MYS-25 (Nikko)	15
PEG-32 laurate	Kessco ® PEG 1540 ML (Stepan)	16
PEG-32 oleate	Kessco ® PEG 1540 MO (Stepan)	17
PEG-32 stearate	Kessco ® PEG 1540 MS (Stepan)	17
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-40 stearate	Myrj 52, Emerest ® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-55 stearate	Nikkol MYS-55 (Nikko)	18
PEG-100 oleate	Crodet O-100 (Croda)	18.8
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19
PEG-200 oleate	Albunol 200 MO (Taiwan Surf.)	>10
PEG-400 oleate	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10
PEG-600 oleate	Albunol 600 MO (Taiwan Surf)	>10

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1.2 PEG-Fatty Acid Diesters

Polyethylene glycol (PEG) fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Among the surfactants in Table 2, preferred hydrophilic surfactants include PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. Representative PEG-fatty acid diesters are shown in Table 2.

TABLE 2

PEG-Fatty Acid Diester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-4 dilaurate	Mapeg ® 200 DL (PPG), Kessco ® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4 dioleate	Mapeg ® 200 DO (PPG),	6
PEG-4 distearate	Kessco ® 200 DS (Stepan	5
PEG-6 dilaurate	Kessco ® PEG 300 DL (Stepan)	9.8
PEG-6 dioleate	Kessco ® PEG 300 DO (Stepan)	7.2
PEG-6 distearate	Kessco ® PEG 300 DS (Stepan)	6.5
PEG-8 dilaurate	Mapeg ® 400 DL (PPG), Kessco ® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
PEG-8 dioleate	Mapeg ® 400 DO (PPG), Kessco ® PEG 400 DO (Stepan), LIPOPEG 4 DO (Lipo Chem.)	8.8
PEG-8 distearate	Mapeg ® 400 DS (PPG), CDS 400 (Nikkol)	11
PEG-10 dipalmitate	Polyaldo 2PKPG	>10
PEG-12 dilaurate	Kessco ® PEG 600 DL (Stepan)	11.7
PEG-12 distearate	Kessco ® PEG 600 DS (Stepan)	10.7
PEG-12 dioleate	Mapeg ® 600 DO (PPG), Kessco ® 600 DO (Stepan)	10
PEG-20 dilaurate	Kessco ® PEG 1000 DL (Stepan)	15
PEG-20 dioleate	Kessco ® PEG 1000 DO (Stepan)	13
PEG-20 distearate	Kessco ® PEG 1000 DS (Stepan)	12
PEG-32 dilaurate	Kessco ® PEG 1540 DL (Stepan)	16
PEG-32 dioleate	Kessco ® PEG 1540 DO (Stepan)	15
PEG-32 distearate	Kessco ® PEG 1540 DS (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 distearate	Cithrol 4DS series (Croda)	>10

1.3 PEG-Fatty Acid Mono- and Di-ester Mixtures

In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown in Table 3.

TABLE 3

PEG-Fatty Acid Mono- and Diester Mixtures

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-150 mono, dilaurate	Kessco ® PEG 200–6000 mono, dilaurate (Stepan)	
PEG 4-150 mono, dioleate	Kessco ® PEG 200–6000 mono, dioleate (Stepan)	
PEG 4-150 mono, distearate	Kessco ® 200–6000 mono, distearate (Stepan)	

1.4 Polyethylene Glycol Glycerol Fatty Acid Esters

Suitable PEG glycerol fatty acid esters are shown in Table 4. Among the surfactants in the Table, preferred hydrophilic surfactants are PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate.

TABLE 4

PEG Glycerol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-20 glyceryl laurate	Tagat ® L (Goldschmidt)	16
PEG-30 glyceryl laurate	Tagat ® L2 (Goldschmidt)	16
PEG-15 glyceryl laurate	Glycerox L series (Croda)	15
PEG-40 glyceryl laurate	Glycerox L series (Croda)	15
PEG-20 glyceryl stearate	Capmul ® EMG (ABITEC), Aldo ® MS-20 KPG (Lonza)	15
PEG-20 glyceryl oleate	Tagat ® O (Goldschmidt)	>10
PEG-30 glyceryl oleate	Tagat ® O2 (Goldschmidt)	>10

1.5. Alcohol-Oil Transesterification Products

A large number of surfactants of different degrees of hydrophobicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohols with a variety of natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, maltol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castor oil (Incrocas-35), PEG-40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylic/capric glycerides (Labrasol), and PEG-6 caprylic/capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS), PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS), PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and PEG-20 almond glycerides (Crovol A40). The latter two surfactants are reported to have HLB values of 10, which is generally considered to be the approximate border line between hydrophilic and hydrophobic surfactants. For purposes of the present invention, these two surfactants are considered to be hydrophobic. Representative surfactants of this class suitable for use in the present invention are shown in Table 5.

TABLE 5

Transesterification Products of Oils and Alcohols

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6–7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 castor oil	Emulgante EL23	>10
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls ® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11
PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls ® EL 719 (Rhone-Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Eumulgin ® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
PEG-100 castor oil	Thornley	>10
PEG-200 castor oil	Eumulgin ® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simusol ® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11
PEG-25 hydrogenated castor oil	Simulsol ® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 hydrogenated castor oil	Cerex ELS 450 (Auschem Spa)	14
PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko); Cremophor RH 60 (BASF)	15
PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15
PEG-100 hydrogenated castor oil	Nikkol HCO-100 (Nikko)	17
PEG-6 corn oil	Labrafil ® M 2125 CS (Gattefosse)	4
PEG-6 almond oil	Labrafil ® M 1966 CS (Gattefosse)	4
PEG-6 apricot kernel oil	Labrafil ® M 1944 CS (Gattefosse)	4
PEG-6 olive oil	Labrafil ® M 1980 CS (Gattefosse)	4
PEG-6 peanut oil	Labrafil ® M 1969 CS (Gattefosse)	4
PEG-6 hydrogenated palm kernel oil	Labrafil ® M 2130 BS (Gattefosse)	4
PEG-6 palm kernel oil	Labrafil ® M 2130 CS (Gattefosse)	4
PEG-6 triolein	Labrafil ® M 2735 CS (Gattefosse)	4
PEG-8 corn oil	Labrafil ® WL 2609 BS (Gattefosse)	6–7
PEG-20 corn glycerides	Crovol M40 (Croda)	10
PEG-20 almond glycerides	Crovol A40 (Croda)	10
PEG-25 trioleate	TAGAT ® TO (Goldschmidt)	11
PEG-40 palm kernel oil	Crovol PK-70	>10
PEG-60 corn glycerides	Crovol M70 (Croda)	15
PEG-60 almond glycerides	Crovol A70 (Croda)	15
PEG-4 caprylic/capric triglyceride	Labrafac ® Hydro (Gattefosse),	4–5
PEG-8 caprylic/capric glycerides	Labrasol (Gattefosse), Labrafac CM 10 (Gattefosse)	>10
PEG-6 caprylic/capric glycerides	SOFTIGEN ® 767 (Huls), Glycerox 767 (Croda)	19
Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10
Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10
Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10
Pentaerythrityl tetracaprylate/tetracaprate	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
Pentaerythrityl tetraoctanoate	Nikkol Pentarate 408 (Nikko)	

Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS, available from Eastman), are also suitable surfactants.

1.6. Polyglycerized Fatty Acids

Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Among the polyglyceryl fatty acid esters, preferred hydrophobic surfactants include polyglyceryl oleate (Plurol Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), and polyglyceryl-10 trioleate. Preferred hydrophilic surfactants include polyglyceryl-10 laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (Caprol® PEG 860). Polyglyceryl polyricinoleates (Polymuls) are also preferred hydrophilic and hydrophobic surfactants. Examples of suitable polyglyceryl esters are shown in Table 6.

TABLE 6

Polyglycerized Fatty Acids

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Polyglyceryl-2 stearate	Nikkol DGMS (Nikko)	5–7
Polyglyceryl-2 oleate	Nikkol DGMO (Nikko)	5–7
Polyglyceryl-2 isostearate	Nikkol DGMIS (Nikko)	5–7
Polyglyceryl-3 oleate	Caprol ® 3GO (ABITEC), Drewpol 3-1-O (Stepan)	6.5
Polyglyceryl-4 oleate	Nikkol Tetraglyn 1-O (Nikko)	5–7
Polyglyceryl-4 stearate	Nikkol Tetraglyn 1-S (Nikko)	5–6
Polyglyceryl-6 oleate	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9
Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14
Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12
Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	>8
Polyglyceryl-10 linoleate	Nikkol Decaglyn 1-LN (Nikko)	12
Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn 5-O (Nikko)	<10
Polyglyceryl-3 dioleate	Cremophor GO32 (BASF)	<10
Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
Polyglyceryl-6 dioleate	Caprol ® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7
Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
Polyglyceryl-10 septaoleate	Nikkol Decaglyn 7-O (Nikko)	3
Polyglyceryl-10 tetraoleate	Caprol ® 10G4O (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-1S (Nikko)	<10
Polyglyceryl-101 decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
Polyglyceryl-10 mono, dioleate	Caprol ® PGE 860 (ABITEC)	11
Polyglyceryl polyricinoleate	Polymuls (Henkel)	3–20

1.7. Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. In this surfactant class, preferred hydrophobic surfactants include propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls), propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex® 200), and propylene glycol dioctanoate (Captex® 800). Examples of surfactants of this class are given in Table 7.

Table 7 includes both mono- and diesters of propylene glycol, and both may be used in one embodiment of the pharmaceutical systems of the present invention. In another embodiment, the absorption enhancing composition is free of both triglycerides and propylene glycol diesters.

1.8. Mixtures of Propylene Glycol Esters—Glycerol Esters

In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are

TABLE 7

Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Propylene glycol monocaprylate	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Propylene glycol monolaurate	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
Propylene glycol myristate	Mirpyl	<10
Propylene glycol monostearate	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo ® PGHMS (Lonza)	3–4
Propylene glycol hydroxy stearate		<10
Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
Propylene glycol isostearate		<10
Propylene glycol monooleate	Myverol P-O6 (Eastman)	<10
Propylene glycol dicaprylate/dicaprate	Captex ® 200 (ABITEC), Miglyol ® 840 (Hüls), Neobee ® M-20 (Stepan)	>6
Propylene glycol dioctanoate	Captex ® 800 (ABITEC)	>6
Propylene glycol caprylate/caprate	LABRAFAC PG (Gattefosse)	>6
Propylene glycol dilaurate		>6
Propylene glycol distearate	Kessco ® PGDS (Stepan)	>6
Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

suitable and are commercially available. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants are shown in Table 8.

TABLE 8

Glycerol/Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Oleic	ATMOS 300, ARLACEL 186 (ICI)	3–4
Stearic	ATMOS 150	3–4

1.9. Mono- and Diglycerides

A particularly important class of surfactants is the class of mono- and diglycerides. These surfactants are generally hydrophobic. Preferred hydrophobic surfactants in this class of compounds include glyceryl monooleate (Peceol), glyceryl ricinoleate, glyceryl laurate, glyceryl dilaurate (Capmul® GDL), glyceryl dioleate (Capmul® GDO), glyceryl mono/dioleate (Capmul® GMO-K), glyceryl caprylate/caprate (Capmul® MCM), caprylic acid mono/diglycerides (Imwitor® 988), and mono- and diacetylated monoglycerides (Myvacet® 9–45). Examples of these surfactants are given in Table 9.

TABLE 9

Mono- and Diglyceride Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Monopalmitolein (C16:1)	(Larodan)	<10
Monoelaidin (C18:1)	(Larodan)	<10
Monocaproin (C6)	(Larodan)	<10
Monocaprylin	(Larodan)	<10
Monocaprin	(Larodan)	<10
Monolaurin	(Larodan)	<10
Glyceryl monomyristate (C14)	Nikkol MGM (Nikko)	3–4
Glyceryl monooleate (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3–4
Glyceryl monooleate	RYLO series (Danisco), DIMODAN series (Danisco), EMULDAN (Danisco), ALDO ® MO FG (Lonza), Kessco GMO (Stepan), MONOMULS ® series (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOrphic 80 (Eastman), ADM DMG-40, 70, and 100 (ADM), Myverol (Eastman)	3–4
Glycerol monooleate/linoleate	OLICINE (Gattefosse)	3–4
Glycerol monolinoleate	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)	3–4
Glyceryl ricinoleate	Softigen ® 701 (Hüls), HODAG GMR-D (Calgene), ALDO ® MR (Lonza)	6
Glyceryl monolaurate	ALDO ® MLD (Lonza), Rodag GML (Calgene)	6.8
Glycerol monopalmitate	Emalex GMS-P (Nihon)	4
Glycerol monostearate	Capmul ® GMS (ABITEC), Myvaplex (Eastman), IMWITOR ® 191 (Hüls), CUTINA GMS, Aldo ® MS (Lonza), Nikkol MGS series (Nikko)	5–9
Glyceryl mono-,dioleate	Capmul ® GMO-K (ABITEC)	<10
Glyceryl palmitic/stearic	CUTINA MD-A, ESTAGEL-G18	<10
Glyceryl acetate	Lamegin ® EE (Grünau GmbH)	<10
Glyceryl laurate	Imwitor ® 312 (Hüls), Monomuls ® 90-45 (Grünau GmbH), Aldo ® MLD (Lonza)	4
Glyceryl citrate/lactate/oleate/linoleate	Imwitor ® 375 (Hüls)	<10
Glyceryl caprylate	Imwitor ® 308 (Hüls), Capmul ® MCMC8 (ABITEC)	5–6
Glyceryl caprylate/caprate	Capmul ® MCM (ABITEC)	5–6
Caprylic acid mono, diglycerides	Imwitor ® 988 (Hüls)	5–6
Caprylic/capric glycerides	Imwitor ® 742 (Hüls)	<10
Mono-and diacetylated monoglycerides	Myvacet ® 9-45, Myvacet ® 9-40, Myvacet ® 9-08 (Eastman), Lamegin ® (Grünau)	3.8–4
Glyceryl monostearate	Aldo ® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor ® 191 (Hüls), Myvaplex (Eastman)	4.4
Lactic acid esters of mono, diglycerides	LAMEGIN GLP (Henkel)	<10
Dicaproin (C6)	(Larodan)	<10
Dicaprin (C10)	(Larodan)	<10
Dioctanoin (C8)	(Larodan)	<10
Dimyristin (C14)	(Larodan)	<10
Dipalmitin (C16)	(Larodan)	<10
Distearin	(Larodan)	<10
Glyceryl dilaurate (C12)	Capmul ® GDL (ABITEC)	3–4
Glyceryl dioleate	Capmul ® GDO (ABITEC)	3–4

TABLE 9-continued

Mono- and Diglyceride Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Glycerol esters of fatty acids	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse)	1
	GELUCIRE 37/06 (Gattefosse)	6
Dipalmitolein (C16:1)	(Larodan)	<10
1,2 and 1,3-diolein (C18:1)	(Larodan)	<10
Dielaidin (C18:1)	(Larodan)	<10
Dilinolein (C18:2)	(Larodan)	<10

1.10 Sterol and Sterol Derivatives

Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is cholesterol. A preferred hydrophilic surfactant in this class is PEG-24 cholesterol ether (Solulan C-24). Examples of surfactants of this class are shown in Table 10.

TABLE 10

Sterol and Sterol Derivative Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Cholesterol, sitosterol, lanosterol		<10
PEG-24 cholesterol ether	Solulan C-24 (Amerchol)	>10
PEG-30 cholestanol	Nikkol DHC (Nikko)	>10
Phytosterol	GENEROL series (Henkel)	<10
PEG-25 phyto sterol	Nikkol BPSH-25 (Nikko)	>10
PEG-5 soya sterol	Nikkol BPS-5 (Nikko)	<10
PEG-10 soya sterol	Nikkol BPS-10 (Nikko)	<10

TABLE 10-continued

Sterol and Sterol Derivative Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-20 soya sterol	Nikkol BPS-20 (Nikko)	<10
PEG-30 soya sterol	Nikkol BPS-30 (Nikko)	>10

1.11. Polyethylene Glycol Sorbitan Fatty Acid Esters

A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several hydrophobic surfactants of this class can be used. Among the PEG-sorbitan fatty acid esters, preferred hydrophilic surfactants include PEG-20 sorbitan monolaurate (Tween-20), PEG-20 sorbitan monopalmitate (Tween-40), PEG-20 sorbitan monostearate (Tween-60), and PEG-20 sorbitan monooleate (Tween-80). Examples of these surfactants are shown in Table 11.

TABLE 11

PEG-Sorbitan Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10 sorbitan laurate	Liposorb L-10 (Lipo Chem.)	>10
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-4 sorbitan monolaurate	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
PEG-80 sorbitan monolaurate	Rodag PSML-80 (Calgene); T-Maz 28	>10
PEG-6 sorbitan monolaurate	Nikkol GL-1 (Nikko)	16
PEG-20 sorbitan monopalmitate	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-4 sorbitan monostearate	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9.6
PEG-8 sorbitan monostearate	DACOL MSS (Condea)	>10
PEG-6 sorbitan monostearate	Nikkol TS106 (Nikko)	11
PEG-20 sorbitan tristearate	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
PEG-6 sorbitan tetrastearate	Nikkol GS-6 (Nikko)	3
PEG-60 sorbitan tetrastearate	Nikkol GS-460 (Nikko)	13
PEG-5 sorbitan monooleate	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
PEG-6 sorbitan monooleate	Nikkol TO-106 (Nikko)	10
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15
PEG-40 sorbitan oleate	Emalex ET 8040 (Nihon Emulsion)	18
PEG-20 sorbitan trioleate	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
PEG-6 sorbitan tetraoleate	Nikkol GO-4 (Nikko)	8.5
PEG-30 sorbitan tetraoleate	Nikkol GO-430 (Nikko)	12
PEG-40 sorbitan tetraoleate	Nikkol GO-440 (Nikko)	13
PEG-20 sorbitan monoisostearate	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
PEG sorbitol hexaoleate	Atlas G-1086 (ICI)	10
PEG-6 sorbitol hexastearate	Nikkol GS-6 (Nikko)	3

1.12. Polyethylene Glycol Alkyl Ethers

Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Preferred hydrophobic ethers include PEG-3 oleyl ether (Volpo 3) and PEG-4 lauryl ether (Brij 30). Examples of these surfactants are shown in Table 12.

TABLE 12

Polyethylene Glycol Alkyl Ethers

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-2 oleyl ether, oleth-2	Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether, oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleyl ether, oleth-5	Volpo 5 (Croda)	<10
PEG-10 oleyl ether, oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether, oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether, laureth-4	Brij 30 (Atlas/ICI)	9.7
PEG-9 lauryl ether		>10
PEG-23 lauryl ether, laureth-23	Brij 35 (Atlas/ICI)	17
PEG-2 cetyl ether	Brij 52 (ICI)	5.3
PEG-10 cetyl ether	Brij 56 (ICI)	13
PEG-20 cetyl ether	Brij 58 (ICI)	16
PEG-2 stearyl ether	Brij 72 (ICI)	4.9
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-20 stearyl ether	Brij 78 (ICI)	15
PEG-100 stearyl ether	Brij 700 (ICI)	>10

1.13. Sugar Esters

Esters of sugars are suitable surfactants for use in the present invention. Preferred hydrophilic surfactants in this class include sucrose monopalmitate and sucrose monolaurate. Examples of such surfactants are shown in Table 13.

TABLE 13

Sugar Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sucrose distearate	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Sucrose distearate/monostearate	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Sucrose dipalmitate		7.4
Sucrose monostearate	Crodesta F-160 (Croda)	15
Sucrose monopalmitate	SUCRO ESTER 15 (Gattefosse)	>10
Sucrose monolaurate	Saccharose monolaurate 1695 (Mitsubishi-Kasei)	15

1.14. Polyethylene Glycol Alkyl Phenols

Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown in Table 14.

TABLE 14

Polyethylene Glycol Alkyl Phenol Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10-100 nonyl phenol	Triton X series (Rohm & Haas), Igepal CA series (GAF, USA), Antarox CA series (GAF, UK)	>10
PEG-15-100 octyl phenol ether	Triton N-series (Rohm & Haas), Igepal CO series (GAF, USA), Antarox CO series (GAF, UK)	>10

1.15. Polyoxyethylene-Polyoxypropylene Block Copolymers

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and hydrophobic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic® series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

Preferred hydrophilic surfactants of this class include Poloxamers 108, 188, 217, 238, 288, 338, and 407. Preferred hydrophobic surfactants in this class include Poloxamers 124, 182, 183, 212, 331, and 335.

Examples of suitable surfactants of this class are shown in Table 15. Since the compounds are widely available, commercial sources are not listed in the Table. The compounds are listed by generic name, with the corresponding "a" and "b" values.

TABLE 15

POE-POP Block Copolymers

COMPOUND	a, b values in $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_3H$		HLB
Poloxamer 105	a = 1	b = 16	8
Poloxamer 108	a = 46	b = 16	>10
Poloxamer 122	a = 5	b = 21	3
Poloxamer 123	a = 7	b = 21	7
Poloxamer 124	a = 11	b = 21	>7
Poloxamer 181	a = 3	b = 30	
Poloxamer 182	a = 8	b = 30	2
Poloxamer 183	a = 10	b = 30	
Poloxamer 184	a = 13	b = 30	
Poloxamer 185	a = 19	b = 30	
Poloxamer 188	a = 75	b = 30	29
Poloxamer 212	a = 8	b = 35	
Poloxamer 215	a = 24	b = 35	
Poloxamer 217	a = 52	b = 35	
Poloxamer 231	a = 16	b = 39	
Poloxamer 234	a = 22	b = 39	
Poloxamer 235	a = 27	b = 39	
Poloxamer 237	a = 62	b = 39	24
Poloxamer 238	a = 97	b = 39	
Poloxamer 282	a = 10	b = 47	
Poloxamer 284	a = 21	b = 47	
Poloxamer 288	a = 122	b = 47	>10
Poloxamer 331	a = 7	b = 54	0.5
Poloxamer 333	a = 20	b = 54	
Poloxamer 334	a = 31	b = 54	
Poloxamer 335	a = 38	b = 54	
Poloxamer 338	a = 128	b = 54	
Poloxamer 401	a = 6	b = 67	
Poloxamer 402	a = 13	b = 67	
Poloxamer 403	a = 21	b = 67	
Poloxamer 407	a = 98	b = 67	

1.16. Sorbitan Fatty Acid Esters

Sorbitan esters of fatty acids are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, and sorbitan tristearate. Examples of these surfactants are shown in Table 16.

TABLE 16

Sorbitan Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7
Sorbitan trioleate	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4.3
Sorbitan sesquioleate	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3.7
Sorbitan tristearate	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2.1
Sorbitan monoisostearate	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4.7
Sorbitan sesquistearate	Nikkol SS-15 (Nikko)	4.2

1.17. Lower Alcohol Fatty Acid Esters

Esters of lower alcohols (C_2 to C_4) and fatty acids (C_8 to C_{18}) are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include ethyl oleate (Crodamol EO), isopropyl myristate (Crodamol IPM), and isopropyl palmitate (Crodamol IPP). Examples of these surfactants are shown in Table 17.

TABLE 17

Lower Alcohol Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Ethyl oleate	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Isopropyl myristate	Crodamol IPM (Croda)	<10
Isopropyl palmitate	Crodamol IPP (Croda)	<10
Ethyl linoleate	Nikkol VF-E (Nikko)	<10
Isopropyl linoleate	Nikkol VF-IP (Nikko)	<10

1.18. Ionic Surfactants

Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. Preferred anionic surfactants include fatty acid salts and bile salts. Preferred cationic surfactants include carnitines. Specifically, preferred ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate; lauroyl carnitine; palmitoyl carnitine; and myristoyl carnitine. Examples of such surfactants are shown in Table 18. For simplicity, typical counterions are shown in the entries in the Table. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion may be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as alkali metal cations or ammonium. Unlike typical non-ionic surfactants, these ionic surfactants are generally available as pure compounds, rather than commercial (proprietary) mixtures. Because these compounds are readily available from a variety of commercial suppliers, such as Aldrich, Sigma, and the like, commercial sources are not generally listed in the Table.

TABLE 18

Ionic Surfactants

COMPOUND	HLB
FATTY ACID SALTS	>10
Sodium caproate	
Sodium caprylate	

TABLE 18-continued

Ionic Surfactants

COMPOUND	HLB
Sodium caprate	
Sodium laurate	
Sodium myristate	
Sodium myristolate	
Sodium palmitate	
Sodium palmitoleate	
Sodium oleate	18
Sodium ricinoleate	
Sodium linoleate	
Sodium linolenate	
Sodium stearate	
Sodium lauryl sulfate (dodecyl)	40
Sodium tetradecyl sulfate	
Sodium lauryl sarcosinate	
Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)]	
BILE SALTS	>10
Sodium cholate	
Sodium taurocholate	
Sodium glycocholate	
Sodium deoxycholate	
Sodium taurodeoxycholate	
Sodium glycodeoxycholate	
Sodium ursodeoxycholate	
Sodium chenodcoxycholate	
Sodium taurochenodeoxycholate	
Sodium glyco cheno deoxycholate	
Sodium cholylsarcosinate	
Sodium N-methyl taurocholate	
Sodium lithocholate	
PHOSPHOLIPIDS	
Egg/Soy lecithin [Epikuron ™ (Lucas Meyer), Ovothin ™ (Lucas Meyer)]	
Lyso egg/soy lecithin	
Hydroxylated lecithin	
Lysophosphatidylcholine	
Cardiolipin	
Sphingomyelin	
Phosphatidylcholine	
Phosphatidyl ethanolamine	
Phosphatidic acid	
Phosphatidyl glycerol	
Phosphatidyl serine	
PHOSPHORIC ACID ESTERS	
Diethanolammonium polyoxyethylene-10 oleyl ether phosphate	
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride	
CARBOXYLATES	
Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates)	
Succinylated monoglycerides [LAMEGIN ZE (Henkel)]	
Sodium stearyl fumarate	
Stearoyl propylene glycol hydrogen succinate	
Mono/diacetylated tartaric acid esters of mono- and diglycerides	
Citric acid esters of mono-, diglycerides	
Glyceryl-lacto esters of fatty acids (CFR ref. 172.852)	
Acyl lactylates:	
lactylic esters of fatty acids	
calcium/sodium stearoyl-2-lactylate	
calcium/sodium stearoyl lactylate	
Alginate salts	
Propylene glycol alginate	
SULFATES AND SULFONATES	
Ethoxylated alkyl sulfates	
Alkyl benzene sulfones	
α-olefin sulfonates	
Acyl isethionates	
Acyl taurates	
Alkyl glyceryl ether sulfonates	
Octyl sulfosuccinate disodium	

TABLE 18-continued

Ionic Surfactants

COMPOUND	HLB
Disodium undecylenamideo-MEA-sulfosuccinate	
CATIONIC Surfactants	>10
Lauroyl carnitine	
Palmitoyl carnitine	
Myristoyl carnitine	
Hexadecyl triammonium bromide	
Decyl trimethyl ammonium bromide	
Cetyl trimethyl ammonium bromide	
Dodecyl ammonium chloride	
Alkyl benzyldimethylammonium salts	
Diisobutyl phenoxyethoxydimethyl benzylammonium salts	
Alkylpyridinium salts	
Betaines (trialkylglycine):	
Lauryl betaine (N-lauryl,N,N-dimethylglycine)	
Ethoxylated amines:	
Polyoxyethylene-15 coconut amine	

1.19 Ionizable Surfactants

Ionizable surfactants, when present in their un-ionized (neutral, non-salt) form, are hydrophobic surfactants suitable for use in the compositions and methods of the present invention, and in their ionized form, are hydrophilic surfactants suitable for use in the present invention. Particular examples of such surfactants include free fatty acids, particularly C_6–C_{22} fatty acids, and bile acids. More specifically, suitable unionized ionizable surfactants include the free fatty acid and bile acid forms of any of the fatty acid salts and bile salts shown in Table 18. Preferred ionizable surfactants include fatty acids and their corresponding salts, such as caprylic acid/sodium caprylate, oleic acid/sodium oleate, capric acid/sodium caprate; ricinoleic acid/sodium ricinoleate, linoleic acid/sodium linoleate, and lauric acid/sodium laurate; trihydroxy bile acids and their salts, such as cholic acid (natural), glycocholic acid and taurocholic acid; dihydroxy bile acids and their salts, such as deoxycholic acid (natural), glycodeoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid (natural), glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid, tauroursodeoxycholic acid, and glycoursodeoxycholic acid; monohydroxy bile acids and their salts, such as lithocholic acid (natural); sulfated bile salt derivatives; sarchocholate; fusidic acid and its derivatives; phospholipids, such as phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, PD inisitol, lysolecithin, and palmitoyl lysophosphatidyl choline; carnitines, such as palmitoyl carnitine, lauroyl carnitine and myristoyl carnitine; cyclodextrins, including alpha, beta and gamma cyclodextrins; and modified cyclodextrins, such as hydroxy propyl and sulfobutyl ether.

1.20 Preferred Surfactants and Surfactant Combinations

Among the above-listed surfactants, several combinations are preferred. In all of the preferred combinations, the absorption enhancing composition includes at least one hydrophilic surfactant. Preferred non-ionic hydrophilic surfactants include alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters: polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydroge-

nated vegetable oils; reaction mixtures of polyols with fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

More preferably, the non-ionic hydrophilic surfactant is selected from the group consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a mixture.

Also preferred are non-ionic hydrophilic surfactants that are reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils or sterols. These reaction mixtures are largely composed of the transesterification products of the reaction, along with often complex mixtures of other reaction products. The polyol is preferably glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

Several particularly preferred absorption enhancing compositions are those which include as a non-ionic hydrophilic surfactant PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG- 100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, or a poloxamer.

Among these preferred surfactants, more preferred are PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. Most preferred are PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, and hydrophilic poloxamers.

The hydrophilic surfactant can also be, or include as a component, an ionic surfactant, i.e., the ionized form of an ionizable surfactant. Preferred ionic surfactants include the ionized form of alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fusidic acid and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-, diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; carnitines; and mixtures thereof.

More preferable ionized ionizable surfactants include the ionized form of bile acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-, diacetylated tartaric acid esters of mono-,diglycerides, succinylated monoglycerides; citric acid esters of mono-, diglycerides; carnitines; and mixtures thereof.

More specifically, preferred ionized ionizable surfactants are the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

Particularly preferred ionized ionizable surfactants are the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof, with the most preferred ionic surfactants being lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof.

The absorption enhancing compositions include at least two surfactants, at least one of which is hydrophilic. In one embodiment, the present invention includes at two surfactants that are hydrophilic, and preferred hydrophilic surfactants are listed above. In another embodiment, the composition includes at least one hydrophilic surfactant and at least one hydrophobic surfactant.

In this embodiment, the hydrophobic surfactant can be an unionized ionizable surfactant. Preferably, the unionized ionizable surfactant is the unionized form of a surfactant

selected from the group consisting of bile acids and analogues and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid esters; alkylsulfates; fatty acids; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-, diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; and mixtures thereof.

More preferably, the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, lycodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid, lithocholic acid, tauroursodeoxycholic acid, glycoursodeoxycholic acid, cholylsarcosine, N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic acid, stearic acid, lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

Still more preferably, the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid, cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric acid, oleic acid, lauryl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

Most preferably, the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurocholic acid, caprylic acid, capric acid, oleic acid, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

The hydrophobic surfactants can also be alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; and the un-ionized (neutral) forms of ionizable surfactants.

As with the hydrophilic surfactants, hydrophobic surfactants can be reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

Preferably, the hydrophobic surfactant is selected from the group consisting of fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; and reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

More preferred are lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof, with glycerol fatty acid esters and acetylated glycerol fatty acid esters being most preferred. Among the glycerol fatty acid esters, the esters are preferably mono- or diglycerides, or mixtures of mono- and diglycerides, where the fatty acid moiety is a C_6 to C_{22} fatty acid.

Also preferred are hydrophobic surfactants which are the reaction mixture of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols. Preferred polyols are polyethylene glycol, sorbitol, propylene glycol, and pentaerythritol.

Specifically preferred hydrophobic surfactants include myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{20} fatty acid; monoglycerides of C_6 to C_{20} fatty acids; acetylated monoglycerides of C_6 to C_{20} fatty acids; diglycerides of C_6 to C_{20} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linolcate; isopropyl linoleate; and poloxamers.

Among the specifically preferred hydrophobic surfactants, most preferred are oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated

monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; and poloxamers.

2. Therapeutic Agents

The hydrophilic therapeutic agents suitable for use in the pharmaceutical systems and methods of the present invention are not particularly limited, as the absorption enhancing compositions are surprisingly capable of delivering a wide variety of hydrophilic therapeutic agents. Suitable hydrophilic therapeutic agents include hydrophilic drugs (i.e., conventional non-peptidic drugs), hydrophilic macromolecules such as cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides and genetic material, and other hydrophilic compounds, such as nucleic acids. The aqueous solubility of the hydrophilic therapeutic agent should be greater than about 1 mg/mL.

The hydrophilic therapeutic agent can be solubilized or suspended in a preconcentrate (before dilution with an aqueous diluent), added to the preconcentrate prior to dilution, added to the diluted preconcentrate, or added to an aqueous diluent prior to mixing with the preconcentrate. The hydrophilic therapeutic agent can also be co-administered as part of an independent dosage form, for therapeutic effect. Optionally, the hydrophilic therapeutic agent can be present in a first, solubilized amount, and a second, non-solubilized (suspended) amount. Such hydrophilic therapeutic agents can be any agents having therapeutic or other value when administered to an animal, particularly to a mammal, such as drugs, nutrients, cosmetics (cosmeceuticals), and diagnostic agents. It should be understood that while the invention is described with particular reference to its value for oral dosage forms, the invention is not so limited. Thus, hydrophilic drugs, nutrients, cosmetics and diagnostic agents which derive their therapeutic or other value from, for example, transmembrane (transport across a membrane barrier of therapeutic significance), nasal, buccal, rectal, vaginal or pulmonary administration, are still considered to be suitable for use in the present invention.

Specific non-limiting examples of therapeutic agents that can be used in the pharmaceutical compositions of the present invention include analgesics and anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents and immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic, sedatives, hypnotics and neuroleptics, β-Blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastrointestinal agents, histamine H_1-receptor antagonists, keratolytics, lipid regulating agents, muscle relaxants, anti-anginal agents, nutritional agents, analgesics, sex hormones, stimulants, cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides and genetic material, and nucleic acids. Amphiphilic therapeutic agents are also included, provided they have a water solubility of greater than about 1 mg/mL.

In one embodiment, the hydrophilic therapeutic agent is a nutritional agent.

In another embodiment, the hydrophilic therapeutic agent is a cosmeceutical agent.

In another embodiment, the hydrophilic therapeutic agent is a diagnostic agent.

Although the invention is not limited thereby, examples of hydrophilic therapeutic agents suitable for use in the compositions and methods of the present invention include the following preferred compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride; ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladona; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; cephapirin sodium; cholera vaccine; chrionic gonadotropin; cidofovir; cisplatin; cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate; colistimethate sodium; colistin sulfate; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin; diatrizoate megluamine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin; dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin; editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famiciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth hormone- bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; measles virus vaccine; meningococcal vaccine; menotropins; mephenzolate bromide; mesalmine; methanamine; methotrexate; methscopolamine; metformin hydrochloride; metroprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; norfloxacin; octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine; pefloxacin; pentamindine isethionate; pentostatin; pentoxifylline; penciclovir; pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate; plague vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine; solatol; somatostatin; sparfloxacin; spectinomycin;

stavudine; streptokinase; streptozocin; suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trandolapril; trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan; varicella virus vaccine live; vasopressin and vasopessin derivatives; vecoronium bromide; vinbiastin; vincristine; vinorelbine; vitamin B12; warfarin sodium; yellow fever vaccine; zalcitabine; zanamavir; zolandtronate; and zidovudine.

Among the listed hydrophilic therapeutic agents, more preferred therapeutic agents are:

acarbose; acyclovir; atracurium besylate; alendronate; anglucerase; amantadine hydrochloride; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant; azithromycin; calcitonin human; calcitonin salmon; capecitabine; cefazolin sodium; cefonicid sodium; cefoperazone; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; chrionic gonadotropin; cidofovir; cladribine; clindamycin and clindamycin derivatives; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; desmopressin; didanosine; dirithromycin; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; fludarabine; foscaret sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth hormone- Bovine; gentamycin; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; vinfluenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; lamivudine; leucovorin calcium; leuprolide acetate; lincomycin and lincomycin derivatives; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; pancuronium bromide; pentamindine isethionate; pentagastrin; physostigmine salicylate; poliovirus vaccine live (OPV); pyridostigmine bromide; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; somatostatin; spectinomycin; stavudine; streptokinase; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trimetrexate gluconate; trospectinomycin; tumor necrosis factor; typhoid vaccine live; urokinase; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; vinblastin; vincristine; vinorelbine; warfarin sodium; zalcitabine; zanamavir; and zidovudine.

The most preferred hydrophilic therapeutic agents are:

acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin human; calcitonin salmon; ceftriaxone; cefuroxime axetil; chrionic gonadotropin; cromalyn sodium; daltaperin sodium; danaproid; desmopressin; didanosine; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone- Bovine; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine interferon alpha; interferon beta; leuprolide acetate; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; residronate; rimantadine hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis factor; typhoid vaccine live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine; zanamavir and zidovudine.

Of course, salts, metabolic precursors, derivatives and mixtures of therapeutic agents may also be used where desired.

3. Solubilizers

If desired, the pharmaceutical compositions of the present invention can optionally include additional compounds to enhance the solubility of the therapeutic agent or the triglyceride in the composition. Examples of such compounds, referred to as "solubilizers", include:

- alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives;
- ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide);
- amides, such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and polyvinylpyrrolidone;
- esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof;
- and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol monoethyl ether (available from Gattefosse under the trade name Transcutol), and water.

Mixtures of solubilizers are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.

Preferred solubilizers include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

The amount of solubilizer that can be included in compositions of the present invention is not particularly limited. Of course, when such compositions are ultimately administered to a patient, the amount of a given solubilizer is limited to a bioacceptable amount, which is readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example, to maximize the concentration of therapeutic agent, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a concentration of 50%, 100%, 200%, or up to about 400% by weight, based on the weight of the carrier. If desired, very small amounts of solubilizers may also be used, such as 25%, 10%, 5%, 1% or even less. Typically, the solubilizer will be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight or about 10% to about 25% by weight.

4. Concentrations

The components of the absorption enhancing compositions of the present invention are present in amounts such that upon dilution with an aqueous diluent, the carrier forms an aqueous dispersion having a small particle size. The hydrophilic and optional hydrophobic surfactants should be present in amounts sufficient to improve the absorption of the hydrophilic therapeutic agent. It is surprisingly found that relatively large amounts of the surfactants can be used while still maintaining a small particle size upon dilution.

Without wishing to be bound by theory, it is believed that the absorption enhancers present in the compositions are able to enhance absorption by one or more of the following factors: effective presentation of an absorption enhancer to the site of enhancement; modulation of facilitated/active transport; transcellular permeability enhancement through favorable membrane perturbations; inhibition of efflux related transporters; inhibition of lumenal or cellular enzymatic inactivation; paracellular transport enhancement through loosening of tight junctions; induction of specific transporters to facilitate transport; altered biological binding characteristics; reduced degradation of the hydrophilic therapeutic agent; induction of transient water channels; and/or increased partitioning of the hydrophilic therapeutic agent by association with the absorption enhancer. The functionality is believed to be due to a combination of small particle size, appropriate absorption enhancers in amounts chosen to provide small particle size upon dilution, and non-dependence upon lipolysis by avoiding the use of triglycerides. Preferably, diesters of propylene glycol are also avoided.

The presence of at least two surfactants, at least one of which is hydrophilic, is believed to be particularly advantageous to provide better presentation of the absorption enhancing components at the absorption site. For example, the presence of each surfactant is believed to assist the absorption enhancement functionality of the other surfactants by reducing the size of the particles containing the absorption enhancing surfactant to minimize aqueous boundary layer control, and/or by solubilizing water-immicible absorption enhancing surfactants to increase the thermodynamic activity of the surfactant at the absorption site.

A preferred method of assessing the appropriate component concentrations is to quantitatively measure the size of the particles of which the dispersion is composed. These measurements can be performed on commercially available particle size analyzers, such as, for example, a Nicomp particle size analyzer available from Particle Size Systems, Inc., of Santa Barbara, Calif. Using this measure, aqueous dispersions according to the present invention have average particle sizes much smaller than the wavelength of visible light, whereas dispersions containing relative amounts of the components outside the appropriate range have more complex particle size distributions, with much greater average particle sizes. It is desirable that the average particle size be less than about 200 nm, preferably less than about 100, more preferably less than about 50 nm, still more preferably less than about 30 nm, and most preferably less than about 20 nm. It is also preferred that the particle size distribution be mono-modal. These particle sizes can be measured at dilution amounts of 10 to 250-fold or more, preferably about 100 to about 250-fold, as is typical of the dilution expected in the gastrointestinal tract.

In a preferred embodiment, the components of the absorption enhancing compositions are present in amounts such that the aqueous dispersion formed upon dilution with an aqueous medium has a small particle size and is also substantially optically clear. The composition in the preconcentrate form, i.e., before dilution with an aqueous diluent, need not be clear, as it is the clarity upon dilution with an aqueous diluent that is preferred. The dilution can be in vitro or in vivo, and optical clarity should be assessed at dilutions of about 10 to 250-fold or more, preferably about 100 to 250-fold, as is encountered in the gastrointestinal environment. It should be appreciated that where the desired dosage form includes an amount of the hydrophilic therapeutic agent that is suspended, but not solubilized, in the composition, the appropriate concentrations of the other components are determined by the optical clarity of the diluted composition without the suspended therapeutic agent.

In this preferred embodiment, the relative amounts of the components are readily determined by observing the properties of the resultant dispersion; i.e., when the relative amounts are within the preferred range, the resultant aqueous dispersion is optically clear. When the relative amounts are outside the preferred range, the resulting dispersion is visibly "cloudy", resembling a conventional emulsion or multiple-phase system. The optical clarity of the aqueous dispersion can be measured using standard quantitative techniques for turbidity assessment. One convenient procedure to measure turbidity is to measure the amount of light of a given wavelength transmitted by the solution, using, for example, a UV-visible spectrophotometer. Using this measure, optical clarity corresponds to high transmittance, since cloudier solutions will scatter more of the incident radiation, resulting in lower transmittance measurements. If this procedure is used, care should be taken to insure that the composition itself does not absorb light of the chosen wavelength, as any true absorbance necessarily reduces the amount of transmitted light and falsely increases the quantitative turbidity value. In the absence of chromophores at the chosen wavelength, suitable dispersions at a dilution of 100x should have an apparent absorbance of less than about 0.3, preferably less than about 0.2, and more preferably less than about 0.1.

Other methods of characterizing optical clarity known in the art may also be used, and any or all of the available methods may be used to ensure that the resulting aqueous dispersions possess the preferred optical clarity.

In one embodiment, the hydrophilic therapeutic agent is formulated in the dosage form of the absorption enhancing composition, and is present in any amount up to the maximum amount that can be solubilized in the composition. In

another embodiment, the hydrophilic therapeutic agent is present in the dosage form of the absorption enhancing composition in a first amount which is solubilized, and a second amount that remains unsolubilized but dispersed. This may be desirable when, for example, a larger dose of the hydrophilic therapeutic agent is desired. Of course, in this embodiment, the optical clarity or particle size of the resultant aqueous dispersion is determined before the second non-solubilized amount of the hydrophilic therapeutic agent is added. In another embodiment, the hydrophilic therapeutic agent is present in a dosage form separate from the dosage form of the absorption enhancing composition, and the amount of hydrophilic therapeutic agent is any convenient amount that can be formulated in the separate dosage form, such as a therapeutically effective amount. This separate dosage form of the hydrophilic therapeutic agent can be a dosage form of the present invention, or any conventional dosage form, preferably triglyceride free, such as a commercial dosage form.

Other considerations well known to those skilled in the art will further inform the choice of specific proportions of the components. These considerations include the degree of bioacceptability of the compounds, and the desired dosage of hydrophilic therapeutic agent to be provided.

Keeping the considerations discussed above in mind, it is important that the composition include sufficient amounts of the absorption enhancing components to provide a therapeutically meaningful increase in the rate and/or extent of bioabsorption. Thus, in general the total amount of absorption enhancing components forming the carrier should be at least about 10% by weight, preferably at least about 20%, based on the total weight of the preconcentrate composition. As shown in the examples herein, the total amount of the absorption enhancing components can be far greater than 20%, and these compositions are also within the scope of the present invention.

It is preferred that when the absorption enhancing composition includes at least two surfactants selected from the group consisting of sodium lauryl sulfate, oleic acid, linoleic acid, monoolein, lecithin, lysolecithin, deoxycholate, taurodeoxycholate, glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20, sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether, polyoxyethylene , sorbitan esters, p-t-octylphenoxypolyoxyethylene, N-lauryl-β-D-maltopyranoside, 1-dodecylazacycloheptane-2-azone, and phospholipids, each surfactant is present in an amount of greater than 10% by weight, based on the total weight of the pharmaceutical system.

Alternatively, appropriate coating can be applied to the dosage form to enable sufficient concentration/amount of the absorption enhancing surfactant/therapeutic agent/inhibitor at the site of absorption.

5. Stability

5.1 Enzyme Inhibitors

When the hydrophilic therapeutic agent is subject to enzymatic degradation, the compositions can include an enzyme inhibiting agent as an absorption enhancing agent. Enzyme inhibiting agents are shown for example, in Bernskop-Schnurch, A., "The use of inhibitory agents to overcome enzymatic barrier to perorally administered therapeutic peptides and proteins", *J. Controlled Release* 52, 1–16 (1998), the disclosure of which is incorporated herein by reference.

Generally, inhibitory agents can be divided into the following classes:

Inhibitors that are not based on amino acids, such as P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate;

Amino acids and modified amino acids, such as aminoboronic acid derivatives and n-acetylcysteine;

Peptides and modified peptides, such as bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin, chymostatin, elastatin, bestatin, bosphoramindon, puromycin, cytochalasin potatocarboxy peptidase inhibitor, and amastatin;

Polypeptide protease inhibitors, such as aprotinin (bovine pancreatic trypsin inhibitor), Bowman-Birk inhibitor and soybean trypsin inhibitor, chicken egg white trypsin inhibitor, chicken ovoinhibitor, and human pancreatic trypsin inhibitor;

Complexing agents, such as EDTA, EGTA, 1,10-phenanthroline and hydroxychinoline; and

Mucoadhesive polymers and polymer-inhibitor conjugates, such as polyacrylate derivatives, chitosan, cellulosics, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor.

The choice and levels of the enzyme inhibitor are based on toxicity, specificity of the proteases and the potency of the inhibition. Enteric coated compositions of the present invention protect hydrophilic therapeutic peptides or proteins in a restricted area of drug liberation and absorption, and reduce or even exclude extensive dilution effects. The inhibitor can be suspended or solubilized in the composition preconcentrate, or added to the aqueous diluent or as a beverage.

Without wishing to be bound by theory, it is believed that an inhibitor can function solely or in combination as:

- a competitive inhibitor, by binding at the substrate binding site of the enzyme, thereby preventing the access to the substrate; examples of inhibitors believed to operate by this mechanism are antipain, elastatinal and the Bowman Birk inhibitor;
- a non-competitive inhibitor which can be simultaneously bound to the enzyme site along with the substrate, as their binding sites are not identical; and/or
- a complexing agent due to loss in enzymatic activity caused by deprivation of essential metal ions out of the enzyme structure.

5.2 Water-Free Preconcentrates

In a particular embodiment, the preconcentrate absorption enhancing composition—ie., the composition before dispersion in an aqueous medium—is free of water. Water-free compositions are preferred to increase the physical and/or chemical stability of the composition or of individual components thereof, allowing for longer storage. In addition, water-free compositions offer advantages in processing, such as, for example, ease in encapsulation.

6. Other Additives

Other additives conventionally used in pharmaceutical compositions can be included, and these additives are well known in the art. Such additives include detackifiers, antifoaming agents, buffering agents, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

An acid or a base may be added to the composition to facilitate processing, or to prevent degradation of the hydrophilic therapeutic agent. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium

hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide. diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, and the like. Also suitable are bases which are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Preferred cations include sodium, potassium, lithium, magnesium, calcium and ammonium.

Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

Although a wide variety of absorption enhancing components, solubilizers and additives can be used in the pharmaceutical systems of the present invention, in one embodiment, it is preferred that the composition be water-free in the preconcentrate form. In another embodiment, it is preferred that the composition be free of propylene glycol diesters. In another embodiment, it is preferred that the composition be free of cholesterol. Of course, combinations of these preferred embodiments are also within the scope of the invention, so that the composition may, for example, be free of several or all of water, propylene glycol diesters and cholesterol.

7. Dosage Forms

The pharmaceutical compositions of the present invention can be formulated as a preconcentrate in a liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate. In the diluted form, the diluent can be water, an aqueous solution, a buffer, an organic solvent, a beverage, a juice, or mixtures thereof. If desired, the diluent can include components soluble therein, such as a hydrophilic therapeutic agent, an enzyme inhibitor, solubilizers, additives, and the like.

The compositions can be processed according to conventional processes known to those skilled in the art, such as lyophilization, encapsulation compression, melting, extrusion, balling, drying, chilling, molding, spraying, spray congealing, coating, comminution, mixing, homogenization, sonication, cryopelletization, spheronization, and granulation, to produce the desired dosage form.

The dosage form is not particularly limited. Thus, compositions of the present invention can be formulated as pills, capsules, caplets, tablets, granules, pellets, beads or powders. Granules, pellets, beads and powders can, of course, be further processed to form pills, capsules, caplets or tablets.

The dosage form can be designed for immediate release, controlled release, extended release, delayed release or targeted delayed release. The definitions of these terms are known to those skilled in the art. Furthermore, the dosage form release profile can be effected by a polymeric matrix composition, a coated matrix composition, a multiparticulate composition, a coated multiparticulate composition, an ion-exchange resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition. Without wishing to be bound by theory, it is believed that the release may be effected through favorable diffusion, dissolution, erosion, ion-exchange, osmosis or combinations thereof.

When formulated as a capsule, the capsule can be a hard or soft gelatin capsule, a starch capsule, or a cellulosic capsule. Such dosage forms can further be coated with, for example, a seal coating, an enteric coating, an extended release coating, or a targeted delayed release coating.

The term "extended release coating" as used herein means a coating designed to effect the delivery of a hydrophilic therapeutic agent, an enzyme inhibitor, or the carrier, over an extended period of time. Preferably, the extended release coating is a pH-independent coating formed of, for example, ethyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, acrylic esters, or sodium carboxymethyl cellulose. Various extended release dosage forms can be readily designed by one skilled in art to achieve delivery of a hydrophilic therapeutic agent, an absorption enhancing carrier or an enzyme inhibitor to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

Dosage forms of the compositions of the present invention can also be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to effect release of a hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier in the lower gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, pellets, beads or particles of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier which are themselves coated or uncoated.

The term "enteric coating" as used herein relates to a mixture of pharmaceutically acceptable excipients which is applied to, combined with, mixed with or otherwise added to the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier. The coating may be applied to a compressed or molded or extruded tablet, a gelatin capsule, and/or pellets, beads, granules or particles of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier. The coating mar be applied through an aqueous dispersion or after dissolving in appropriate solvent. Additional additives and their levels, and selection of a primary coating material or materials will depend on the following properties:

1. resistance to dissolution and disintegration in the stomach;

2. impermeability to gastric fluids and drug/carrier/enzyme while in the stomach;
3. ability to dissolve or disintegrate rapidly at the target intestine site;
4. physical and chemical stability during storage;
5. non-toxicity;
6. easy application as a coating (substrate friendly); and,
7. economical practicality.

The term "delayed release" as used herein refers to the delivery of the hydrophilic therapeutic agent, an enzyme inhibitor, and/or the absorption enhancing carrier, which is effected by formulating the composition so that the release can be accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. The preferred method for delay of release is coating. Coating prevents exposure of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier to the epithelial and mucosal tissue of the buccal cavity, pharynx, esophagus, and stomach, and to the enzymes associated with these tissues. This helps to protect the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier and the tissues from any adverse event prior to the delivery at the desired site of absorption. Furthermore, coated compositions of the present invention allow balancing enhancement effectiveness, active protection, and safety liability through coating controlled dilution of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier upon administration through delayed release or sustained release. Multiple enteric coatings targeted to release hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier at various regions in the lower gastrointestinal tract would enable even more effective and sustained improved delivery throughout the lower gastrointestinal tract.

Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier to the lower gastrointestinal tract. The coating chosen should be compatible with the hydrophilic therapeutic agent and the other selected components. The preferred polymers for use in the present invention are anionic carboxylic polymers. The more preferred polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

Shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH>7.

Acrylic polymers (preferred). The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonio methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for extended release. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine.

Cellulose Derivatives (also preferred). Examples of suitable cellulose derivatives are:

ethyl cellulose;

reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH>6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP psuedolatex with particles <1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides;

cellulose acetate trimellitate (Eastman);

methylcellulose (Pharmacoat, Methocel);

hydroxypropyl methyl cellulose phthalate (HPMCP). The performance can vary based on the degree and type of substitution. HP-50, HP-55, HP-55S HP-55F grades are suitable;

hydroxypropyl methyl cellulose succinate (HPMCS; AQOAT (Shin Etsu)).

The performance can vary based on the degree and type of substitution. Suitable grades include AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions;

Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH>5, and it is much less permeable to water vapor and gastric fluids; and

Cotteric (by Colorcon).

Combinations of the above materials can also be used.

The coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include: triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10–25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the lower intestinal tract is reached.

Colorants, detackifiers, surfactants, antifoaming agents, lubricants, stabilizers such as hydroxy propyl cellulose, acid/base may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

A particularly suitable methacrylic copolymer is Eudragit L.RTM, particularly L-30D.RTM and Eudragit 100–55. RTM, manufactured by Rohm Pharma, Germany. In Eudragit L-30 D.RTM, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5–5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract.

Another methacrylic acid polymer which is suitable for use in coating the oral dosage forms and/or the granules, particles, pellets or beads of absorption enhancing carrier and/or hydrophilic therapeutic agent which can be employed in the compositions and methods described herein, either

alone or in combination with other coatings, is Eudragit S.RTM, manufactured by Rohm Pharma, Germany. Eudragit S.RTM. differs from Eudragit L-30-D.RTM only insofar as the ratio of free carboxyl groups to ester groups is approximately 1:2. Eudragit S.RTM is insoluble at pH below 5.5, but unlike Eudragit L-30-D.RTM, is poorly soluble in gastrointestinal fluids having pH of 5.5–7.0, such as is present in the small intestine media. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. Eudragit S.RTM can be used alone as a coating to provide delivery of the hydrophilic therapeutic agent and/or the absorption enhancing carrier beginning at the large intestine via a delayed release mechanism. In addition, Eudragit S.RTM, being poorly soluble in intestinal fluids below pH 7, can be used in combination with Eudragit L-30-D.RTM, soluble in intestinal fluids above pH 5.5, in order to effect a delayed release composition which can be formulated to deliver the hydrophilic therapeutic agent and/or absorption enhancing carrier to various segments of the intestinal tract. The more Eudragit L-30 D.RTM used the more proximal realease and delivery begins, and the more Eudragit S.RTM used, the more distal release and delivery begins Both Eudragit L-30-D-RTM and Eudragit S.RTM can be substituted with other pharmaceutically acceptable polymers with similar pH solubility characteristics.

Preferred materials include shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof. More preferred materials include Eudragit series E, L, S, RL, RS, NE, L.RTM, L300.RTM, S.RTM, 100-55RTM, cellulose acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, poly vinyl acetate phthalate, and Cotteric. Most preferred materials include Eudragit series L.RTM, L300.RTM, S.RTM, L100-55RTM, cellulose acetate phthalate, Aquateric, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, poly vinyl acetate phthalate, and Cotteric.

Extended release and targeted delayed release coatings for dosage forms of the compositions of the present invention are described more completely in U.S. Pat. Nos. 5,622,721 and 5,686,105, the disclosures of which are incorporated herein by reference in their entirety.

Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, buccal, nasal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, as well as for oral administration. Thus, the dosage form can be a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup, elixer, or other dosage form, as desired. If formulated as a suspension, the composition can further be processed in capsule form.

When formulated as a sprayable solution or dispersion, a dosage form of a multiparticulate carrier coated onto a substrate with the pharmaceutical compositions described herein can be used. The substrate can be a granule, a particle, a pellet or a bead, for example, and formed of a therapeutic agent or a pharmaceutically acceptable material. The multiparticulate carrier can be enteric coated with a pharmaceutically acceptable material, such as the targeted delayed enteric coatings and extended release coatings of U.S. Pat. Nos. 5,622,721 and 5,686,105, described above. The multiparticulate carrier, coated or uncoated, can further be processed by encapsulation, and the resultant capsule can also be coated, if desired.

Other additives may be included, such as are well-known in the art, to impart the desired consistency and other properties to the formulation.

8. Specific Embodiments

In all of the embodiments described herein, the components of the absorption enhancing carrier are present in amounts such that upon mixing with an aqueous diluent, either in vitro or in vivo, the carrier forms an aqueous dispersion having a small average particle size. In a preferred embodiment, the dispersion is also substantially optically clear. In these preferred embodiments, the optical clarity or particle size in an aqueous dispersion defines the preferred relative concentrations of the components as described above, but does not restrict the dosage form of the compositions to an aqueous dispersion, nor does it limit the compositions of the invention to optically clear dosage forms. Thus, the preferred concentrations of the components are determined by the particle size and/or optical clarity of a dispersion formed by the composition preconcentrate and an aqueous diluent in a dilution of about 10 to about 250-fold, as a preliminary matter. Once the appropriate concentrations are determined, the pharmaceutical compositions can be formulated as described in the preceding section, without regard to the optical clarity of the ultimate formulation in these preferred embodiments.

In one particular embodiment, the present invention provides a triglyceride-free pharmaceutical system including an absorption enhancing composition including at least two surfactants, at least one of which is hydrophilic. The surfactants are present in amounts such that the carrier forms an aqueous dispersion having a small average particle size. In one preferred aspect of this embodiment, the average particle size is less than about 200 nm upon mixing with an aqueous diluent. In another preferred aspect of this embodiment, the aqueous dispersion is substantially optically clear. Preferably, the composition includes a mixture of hydrophilic and hydrophobic surfactants.

The pharmaceutical system also includes a hydrophilic therapeutic agent. The hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and suspended, in the dosage form of the absorption enhancing composition. Alternatively, the hydrophilic therapeutic agent can be provided in a separate dosage form, so that in use, the dosage form of the absorption-enhancing composition and the dosage form of the hydrophilic therapeutic agent are co-administered. In the latter aspect, the pharmaceutical system can make use of any dosage form of a hydrophilic therapeutic agent, such as commercially available dosage forms. The pharmaceutical system is particularly advantageous, since the absorption enhancing pharmaceutical composition improves the functionality of even conventionally formulated hydrophilic therapeutic agents. Preferably, the dosage form of the absorption enhancing pharmaceutical composition, with or without a hydrophilic therapeutic agent, is an orally administrable dosage form. If the hydrophilic therapeutic agent is provided in a separate dosage form, it is preferred that the dosage form of the hydrophilic therapeutic agent also be an orally administrable dosage form.

In another aspect, the present invention provides a method of improving the bioabsorption of a hydrophilic therapeutic agent administered to a patient, such as an animal, preferably a mammal, and more preferably a human. The method includes the steps of providing a dosage form of an absorption enhancing composition, providing a hydrophilic therapeutic agent, and administering the dosage form of the absorption enhancing composition and the hydrophilic

therapeutic agent to the patient. The dosage form of the absorption enhancing composition can be any of the dosage forms described above. Similarly, the hydrophilic therapeutic agent can be provided solubilized, suspended, or partially solubilized and suspended, in the dosage form of the absorption enhancing composition, or can be provided in a separate dosage form. It is surprisingly found that by administering a hydrophilic therapeutic agent contained within, or co-administered with, a dosage form of an absorption enhancing composition of the present invention, the rate and/or extent, or the consistency in the rate and/or extent of bioabsorption of the hydrophilic therapeutic agent is unexpectedly enhanced. Thus, in one aspect the method increases the rate and/or extent of bioabsorption. In another aspect, the method increases the consistency of the rate and/or extent of bioabsorption. In this latter aspect, the rate and/or extent of bioabsorption can be greater than or less than the rate that would be seen using conventional methods.

In other embodiments, the absorption enhancing compositions in the pharmaceutical systems and methods of the present invention can be free of water in the preconcentrate form, free of propylene glycol diesters, and/or free of cholesterol. All of the compositions, however, are substantially free of triglycerides.

9. Preparation of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention can be prepared by conventional methods well known to those skilled in the art. Of course, the specific method of preparation will depend upon the ultimate dosage form. For dosage forms substantially free of water, i.e., when the composition is provided in a pre-concentrate form for later dispersion in vitro or in vivo in an aqueous system, the composition is prepared by simple mixing of the components to form a pre-concentrate. The mixing process can be aided by gentle heating, if desired. For compositions in the form of an aqueous dispersion, the pre-concentrate form is prepared, then the appropriate amount of an aqueous diluent is added. Upon gentle mixing, an aqueous dispersion is formed. If any water-soluble enzyme inhibitors or additives are included, these may be added first as part of the pre-concentrate, or added later to the aqueous dispersion, as desired. The dosage forms of the absorption enhancing compositions can be prepared with or without a hydrophilic therapeutic agent, and a hydrophilic therapeutic agent may also be provided in the diluent, if desired, or in a separate dosage form.

As previously noted, in another embodiment, the present invention includes a multi-phase dispersion containing a hydrophilic therapeutic agent. In this embodiment, a dosage form includes a hydrophilic therapeutic agent and an absorption enhancing composition which forms an aqueous dispersion upon mixing with an aqueous diluent, and an additional amount of non-solubilized hydrophilic therapeutic agent. Thus, the term "multi-phase" as used herein to describe these compositions of the present invention means a composition which when mixed with an aqueous diluent forms an aqueous phase and a particulate dispersion phase. The composition components are as described above, and can include any of the surfactants, therapeutic agents, solubilizers and additives previously described. An additional amount of hydrophilic therapeutic agent is included in the composition. This additional amount is not solubilized in the composition, and upon mixing with an aqueous system is present as a separate dispersion phase. The additional amount is optionally a milled, micronized, or precipitated form. Thus, upon dilution, the composition contains two phases: an aqueous dispersion phase containing a first, solubilized amount of the hydrophilic therapeutic agent, and a second, non-solubilized amount of the hydrophilic therapeutic agent dispersed therein.

One skilled in the art will appreciate that a hydrophilic therapeutic agent may have a greater solubility in the pre-concentrate composition than in the aqueous dispersion, so that meta-stable, supersaturated solutions having apparent optical clarity but containing a hydrophilic therapeutic agent in an amount in excess of its solubility in the aqueous dispersion can be formed. Such super-saturated solutions, whether characterized as aqueous dispersions (as initially formed) or as multi-phase solutions (as would be expected if the meta-stable state breaks down), are also within the scope of the present invention.

The multi-phase formulation can be prepared by the methods described above. A pre-concentrate is prepared by simple mixing of the components, with the aid of gentle heating, if desired. It is convenient to consider the hydrophilic therapeutic agent as divided into two portions, a first solubilizable portion which will be solubilized and contained within the clear aqueous dispersion upon dilution, and a second non-solubilizable portion which will remain non-solubilized. When the ultimate dosage form is non-aqueous, the first and second portions of the hydrophilic therapeutic agent are both included in the pre-concentrate mixture. When the ultimate dosage form is aqueous, the composition can be prepared in the same manner, and upon dilution in an aqueous system, the composition will form the two phases as described above, with the second non-solubilizable portion of the hydrophilic therapeutic agent dispersed or suspended in the aqueous system, and the first solubilizable portion of the hydrophilic therapeutic agent solubilized in the composition. Alternatively, when the ultimate dosage form is aqueous, the pre-concentrate can be prepared including only the first, solubilizable portion of the hydrophilic therapeutic agent. This pre-concentrate can then be diluted in an aqueous system to form an aqueous dispersion, to which is then added the second, non-solubilizable portion of the hydrophilic therapeutic agent to form a multi-phase aqueous composition.

B. Characteristics of the Pharmaceutical Compositions and Methods

The dispersions formed upon dilution of the pharmaceutical compositions of the present invention are believed to have some or all of the following characteristics:

Rapid formation: upon dilution with an aqueous diluent, the composition forms an aqueous dispersion of small particle size very rapidly; i.e., the dispersion appears to form instantaneously.

Optical clarity: in a preferred embodiment, the dispersions are essentially optically clear to the naked eye, and show no readily observable signs of heterogeneity, such as turbidity or cloudiness. More quantitatively, dispersions of the pharmaceutical compositions of the present invention have absorbances (400 nm) of less than about 0.3, and generally less than about 0.1, at 100× dilution in this preferred embodiment. In the multi-phase embodiment of the compositions described herein, it should be appreciated that the optical clarity of the aqueous phase will be obscured by the dispersed particulate non-solubilized hydrophilic therapeutic agent.

Small Particle Size: dispersions of the pharmaceutical compositions of the present invention contain particles of very small size. Preferably, the average size is less than about 200 nm, more preferably less than about 100 nm, still

more preferably less than about 50 nm and most preferably less than about 20 nm. The small particle size promotes efficient transport of the absorption enhancing components to the absorption site.

Robustness to dilution: the dispersions are surprisingly stable to dilution in aqueous solution. The absorption enhancing composition remains solubilized for at least the period of time relevant for absorption.

The unique pharmaceutical compositions and methods of the present invention present a number of significant and unexpected advantages, including:

Efficient transport: The particle sizes in the aqueous dispersions of the present invention are much smaller than the larger particles characteristic of vesicular, emulsion or microemulsion phases. This reduced particle size enables more efficient transport through the intestinal aqueous boundary layer, and through the absorptive brush border membrane. More efficient transport to absorptive sites leads to improved and more consistent absorption of therapeutic agents. Moreover, the present invention allows absorption enhancing components to be delivered to the absorption site along with the hydrophilic therapeutic agent, to further enhance absorption.

No dependence on lipolysis: The lack of triglycerides provides pharmaceutical compositions that are not dependent upon lipolysis, and upon the many poorly characterized factors which affect the rate and extent of lipolysis, for effective presentation of a therapeutic agent to an absorptive site. Such factors include the presence of composition components which may inhibit lipolysis; patient conditions which limit production of lipase, such as pancreatic lipase secretory diseases; and dependence of lipolysis on stomach pH, endogenous calcium concentration, and presence of co-lipase or other digestion enzymes. The lack of lipolysis dependence further provides transport which is less prone to suffer from any lag time between administration and absorption caused by the lipolysis process, enabling a more rapid onset of therapeutic action and better bioperformance characteristics. In addition, pharmaceutical compositions of the present invention can make use of hydrophilic surfactants which might otherwise be avoided or limited due to their potential lipolysis inhibiting effects.

Non-dependence on bile and meal fat contents: Due to the higher solubilization potential over bile salt micelles, the present compositions are less dependent on endogenous bile and bile related patient disease states, and meal fat contents. These advantages overcome meal-dependent absorption problems caused by poor patient compliance with meal-dosage restrictions.

Faster dissolution and release: Due to the robustness of compositions of the present invention to dilution, the components of the absorption enhancing composition remain solubilized and thus do not suffer problems of precipitation or agglomeration in the time frame relevant for absorption. In addition, the therapeutic agent is presented in small particle carriers, and is not limited in dilution rate by entrapment in emulsion carriers.

Consistent performance: Aqueous dispersions of the present invention are thermodynamically stable for the time period relevant for absorption, and can be more predictably reproduced, thereby limiting variability in bioavailability—a particularly important advantage for therapeutic agents with a narrow therapeutic index.

Less prone to gastric emptying delays: Unlike conventional triglyceride-containing formulations, the present compositions are less prone to gastric emptying delays, resulting in faster absorption. Further, the particles in dispersions of the present invention are less prone to unwanted retention in the gastrointestinal tract.

Better targeted absorption: The compositions of the present invention can be targeted to specific absorption sites through targeted enteric coating or extended release coating, thus minimizing dilution effects and optimizing activity of the hydrophilic therapeutic agent.

These and other advantages of the present invention, as well as aspects of preferred embodiments, are illustrated more fully in the Examples which follow.

EXAMPLES

Example 1

Preparation of Compositions

A simple pre-concentrate is prepared as follows. Predetermined weighed amounts of the components are stirred together to form a homogeneous mixture. For combinations that are poorly miscible, the mixture can be gently heated to aid in formation of the homogeneous mixture. If the composition is to include a hydrophilic therapeutic agent, the chosen hydrophilic therapeutic agent in a predetermined amount can be added and stirred until solubilized. Optionally, solubilizers or additives are included by simple mixing.

To form an aqueous dispersion of the pre-concentrate, a predetermined amount of an aqueous medium such as purified water, buffer solution, or aqueous simulated physiological solution, is added to the pre-concentrate, and the resultant mixture is stirred to form an aqueous dispersion. Of course, when the dosage form is an aqueous dispersion, any of the components that are readily water-soluble, including the hydrophilic therapeutic agent, can be provided in the diluent solution.

Examples 2–3

Membrane Transport and In Situ Absorption Studies

Compositions of the present invention were tested by two different methods, to demonstrate the improved delivery of hydrophilic therapeutic agents incorporated within or co-administered with compositions including an absorption enhancing carrier. In one set of studies, the relative permeability of membranes to hydrophilic therapeutic agents was compared with and without the presence of an absorption enhancing carrier ("Membrane Transport Study"). In a second set of studies, the relative absorption of a hydrophilic therapeutic agent in rat mesenteric veins was compared with and without the presence of an absorption enhancing carrier ("Relative Absorption Study").

For Examples 2 and 3, the following compositions were used, as described in the following sections. For each sample composition, absorbance measurements were made at 400 nm, using a UV-Visible spectrophotometer, at a dilution of 25× with distilled water. In addition, particle size measurements were made using a particle size analyzer, and the volume-weighted average particle sizes are shown along with sample characteristics in Table 19. The standard deviation of the particle size distribution is shown in parentheses next to the average particle size.

TABLE 19

Sample Compositions and Characterizations

Sample No.	Components	Amounts (g)	Absorbance	Size (nm)
1	Cremophor RH40	0.50	0.016	14.1 (2.5)
	Labrasol	0.20		
	Capmul MCM	0.30		
2	Tween 20	0.67	0.039	12.3 (2.1)
	Lauroglycol	0.16		
	Glycofurol	0.17		
3	Cremophor RH40	0.30	0.004	9.0 (1.6)
	Arlacel 186	0.20		
	Sodium taurocholate	0.18		
	Propylene glycol	0.32		
4	Cremophor RH40	0.54	0.167	17.6 (3.8)
	Span 80	0.26		
	PEG 400	0.20		
5	Cremophor RH40	0.06	2.497	2610 (564)
	Arlacel 186	0.62		
	Propylene glycol	0.32		
6	Cremophor RH40	0.49	-0.010	13.8 (2.3)
	Propylene glycol	0.51		

Note that Sample Nos. 5 and 6 are control samples. Sample No. 5 was observed to form a cloudy emulsion upon mixing with an aqueous diluent, and fails to show a small particle size. Sample No. 6 contains only one surfactant.

Example 2

Membrane Transport Studies

Experimental

The membrane transport studies of model hydrophobic therapeutic agents were carried out across the CACO-2 monolayers. The Caco-2 cell line, originating from a human carcinoma, was obtained from the American Type Culture collection and was grown to form confluent monolayers as described elsewhere (I. J. Hidalgo, T. J. Raub, and R. T. Borchardt, *Gastroenterology* 96:736–749 (1989)). All cells used in this study were between 50 and 60 passage number. The cells were measured for confluency by measurement of TEER (trans epithelial electrical resistance) values. Monolayers exhibiting similar TEER values consistent with "non leakiness" were used to study and compare transport characteristics of model actives in plain buffer and in presence of diluted compositions of the present invention.

In duplicate, all transport experiments were performed for 2 hrs at 37° C. in pH 7.35 HBSS containing 25 mM glucose and 10 mM Hepes buffer. Prior to the experiments, the culture medium of Transwell grown Caco-2 cell monolayers was replaced with transport medium equilibrated at 37° C., and the cell monolayer was subsequently equilibrated before undertaking transport studies.

Two hydrophilic therapeutic agents, foscarnet and PEG-4000, were tested. Foscarnet sodium is a low molecular weight (192 g/mol) hydrophilic antiviral that inhibits viral DNA polymerase and reverse transcriptase. It is very soluble in water, shows pK_as of 0.5, 3.4 and 7.3, and has a log of octanol/water partition coefficient of -2.0 (at pH 7.4). Apical to basal transport of the model hydrophilic actives foscarnet sodium and polyethylene glycol 4000 (PEG-4000) was studied by spiking the transport medium, a plain buffer or a 100× buffer dilution of the composition under investigation, with one micro curie of radio-labeled active on the apical side. Basolateral appearance of the active was monitored by taking appropriate samples and assaying for radioactivity. Permeability coefficients (P) were calculated using the following equation:

$$P=(dQ/dt)/(AC_0)$$

where P is the permeability coefficient, dQ/dt is the flux across the monolayer (DPM/min), A is the surface area of the membrane, and C_0 is the initial concentration of the active.

Results:

Table 20 shows the apical to basal membrane transport of a conventional hydrophilic active, foscarnet sodium in Sample Nos. 1–3, and a model macromolecular hydrophilic active, PEG-4000, in Sample No. 4, compared to a plain buffer solution

TABLE 20

Permeability for a Conventional Hydrophilic Active

Sample No.	Active	$(P_{sample}{}^a/P_{buffer}{}^b) \times 100$
1	foscarnet sodium	1007
2	foscarnet sodium	195
3	foscarnet sodium	160
4	PEG-4000	188

[a]permeability in the presence of 100× diluted composition
[b]permeability in the presence of buffer only

Example 3

Relative Absorption Study

Experimental:

The sample preconcentrate solutions were diluted with standard hypotonic PBS pH 7.4 buffer. Two hydrophilic therapeutic agents were studied: a conventional hydrophilic active, acyclovir, and the model macromolecular active, PEG-4000.

For the acyclovir compositions, the compositions after dilution were spiked with 0.1 mM cold acyclovir, then 0.5 microliter of tritiated acyclovir (specific activity 18.9 Ci/mmol) was added to the diluted composition. The osmotic pressure was adjusted with sodium chloride as needed. The resulting aqueous isotonic dispersions were perfused through rat intestinal segments to assess absorption enhancement in a procedure described below. Appearance of the active was monitored in the mesenteric blood along with disappearance on the lumenal side.

Surprisingly, appreciable levels of the conventional hydrophilic active were noted in the blood compared to control perfusion studies conducted with plain buffer and with the control samples 5 (milky emulsion-forming preconcentrate) and 6 (plain one surfactant concentrate), showing that the compositions of the present invention increased absorption characteristics of very hydrophilic actives.

For the model macromolecular active, radio labeled PEG-4000 was added to a diluted (50×) pre-concentrate, and the resulting clear aqueous isotonic dispersion was perfused through a rat intestinal segment to assess absorption enhancement in a procedure described below. Appearance of the active was monitored in the mesenteric blood along with disappearance on the lumenal side. Surprisingly, as with the acyclovir, appreciable levels of hydrophilic active were noted in the blood compared to control perfusion studies conducted with plain buffer, showing the unexpected result that the compositions of the present invention increased permeability characteristics of very hydrophilic macromolecular actives.

Procedure:

Young adult (275–300 g) male Sprague Dawley rats were used. The procedures were consistent with those reported by Winne et al., "In vivo studies of mucosal-serosal transfer in

rat jejunum", *Naunyn-Schmeideberg's Arch. Pharmacol.*, 329, 70 (1985).

Jugular vein cannulation: the animal was anesthetized using 2% halothane in 98% oxygen via a halothane vaporizer (Vapomatic, A.M. Bickford, Inc., N.Y.). An opening in the jugular vein was made with a 21 gauge needle and a jugular cannula consisting of a 4 cm segment of silastic tubing connected to polyethylene tubing was inserted in the jugular vein and secured with cyanoacrylate glue. For the donor rat, approximately 20 mL of blood was freshly collected in the presence of heparin (1,000 units) and the collected blood was infused at a rate of 0.2 mL/min through the jugular vein in the experimental rat to replenish blood sampling.

Intestine cannulation: after the animal was anesthetized, its body temperature was maintained at 37° C. using a heating pad. A vertical midline incision of approximately 3 cm was made through the skin to expose the small intestine. Approximately 6–10 cm segment of ileum was located. Using electro-cautery, a small incision was made at the ends of the segment and the lumenal contents were flushed with saline maintained at 37° C. Two 1.5 cm notched pieces of Teflon tubing were inserted into the intestinal lumen at each incision and tightened using 4-0 silk. A warm isotonic buffer was passed through the intestine using a 50-mL syringe. These teflon cannula were used to perfuse the drug solution through the isolated intestinal segment using a syringe pump.

Mesenteric vein cannulation: the mesenteric vein draining blood from the resulting isolated mesenteric cascade venule was then cannulated using a 24 gauge IV catheter and secured in place using 4-0 silk sutures. The cannula was then connected to a polyethylene tubing 25 cm long where the blood was collected in a vial kept under the animal level. Blood samples were collected continuously over 60 to 90 min. The infusion of blood via the jugular vein was initiated to replenish blood loss.

Results:

I. Conventional Hydrophilic Active (acyclovir)

The experiment was performed twice for each of the test samples and control buffer compositions. For each formulation, the results of the two trials were averaged. The cumulative amount of radioactivity for the duration of the study as a fraction of total radioactivity exposed to the intestinal segment was monitored for each trial to assess absorption. The % relative absorption results for a conventional hydrophilic active (acyclovir) in presence of various diluted example compositions compared to a plain buffer are presented in Table 21. The relative absorption reported in Table 21 is 100 times the ratio of the fraction of the total amount administered in mesenteric blood when perfused with the 25x diluted compositions to the fraction of the total amount administered when perfused with the plain buffer, over the same time period.

TABLE 21

Relative Absorption of Acyclovir

Sample No.	% Relative Absorption
1	614
2	634
3	704
Control Samples:	
5	171
6	141

Surprisingly, appreciable bioenhancement was observed only for compositions that had at least one hydrophilic surfactant plus a second surfactant, and that formed very small dispersions upon dilution (Sample Nos. 1–3), showing that effective presentation of carrier at the absorption site is very critical. In contrast, compositions that contained the same surfactants but formed larger unstable emulsion upon dilution (Sample No. 5) due to poor choice of concentration, or contained only a single surfactant (Sample No. 6) resulted in only marginal bioenhancement over plain buffer.

II. Macromolecular Hydrophilic Active

The results for a macromolecular hydrophilic active is presented in Table 22. The experiment was performed twice for each composition. The relative absorption shown in the Table is for a 50x dilution

TABLE 22

Relative Absorption of a Macromolecular Active

Sample No.	% Relative Absorption
3	991

In comparison to negligible absorption of PEG 4000 in presence of plain buffer, the absorption of PEG 4000 in the presence of a composition of the present invention gave surprising high absorption. This demonstrates the improved absorption of macromolecules with compositions of the present invention.

Example 4

Absorption Enhancing Carriers

Typical surfactant ratios consistent with the invention that can be prepared are listed. Additives can be included as discussed herein, and the concentrations can be varied as desired to render the compositions easy to prepare, stable upon storage, bioacceptable and elegant, provided that the concentrations are such that the carrier forms an aqueous dispersion having a small particle size, upon dilution with an aqueous medium. Adequate enzyme inhibitor, bufferants, other additives and organic solubilizers can be included at pharmaceutically acceptable levels. Hydrophilic therapeutic agents can be added at levels convenient for therapeutic effect.

A: Compositions Having At least Two Hydrophilic Surfactants

Sodium taurocholate	0.18 g
Cremophor RH 40	0.30 g
Sodium chenodeoxycholate	0.30 g
Tween 80	0.50 g
Sodium Sarcocholate	0.15 g
Crovol M-70	0.60 g
Sodium lithocholate	0.30 g
Labrasol	0.55 g
Sodiun glycocholate	0.10 g
Tween 20	0.50 g
Sodium ursodeoxycholate	0.30
Incrocas-35	0.50
Chenodeoxycholic acid	0.25 g
Cremophor RH 40	0.50 g
Cremophor RH 40	0.60 g
Sodium caprate	0.10 g
Cremophor RH 40	0.50 g
Palmitoyl carnitine	0.20 g
Solulan C-24	0.60 g
Sodium chenodeoxycholate	0.25 g
Taurocholate	0.20 g
Egg or Soy lecithin	0.09 g

-continued

Tween 20	0.30 g
Sodium taurocholate	0.20 g
Tween 20	0.25 g
Egg lecithin	0.15 g
Chenodeoxycholate	0.18 g
C_{18} lysolipid	0.10 g
Chenodeoxycholate	0.20 g
Oleic acid	0.10 g
Labrasol	0.20 g
Brij 35	0.75 g

B: Compositions Having One Hydrophilic and One Hydrophobic Surfactant

Cremophor EL-P	0.83 g
Peceol	0.17 g
Cremophor EL-P	0.50 g
Propylene glycol monocaprate	0.20 g
Cremophor EL-P	0.50 g
Imwitor 375	0.20 g
Cremophor EL-P	0.50 g
Nikkol MGM	0.18 g
Cremophor RH 40	0.50 g
Arlacel 186	0.10 g
Cremophor RH 40	1.53 g
Arlacel 186	0.38
HPB cyclodextrin	0.18 g
Cremophor RH 40	0.55 g
Capmul MCM	0.80 g
Cremophor RH 40	0.50 g
Crodamol (ethyl oleate)	0.28 g
Cremophor RH 40	0.50 g
Labrafil	0.40 g
Cremophor RH 40	0.22 g
Lauroglycol FCC	0.20 g
Cremophor RH 40	0.60 g
Glyceryl monolaurate	0.20 g
Cremophor RH-40	0.43 g
Myvacet 9-45	0.31 g
Cremophor RH-40	0.30 g
Peceol	0.11 g
Cremophor RH40	0.50 g
Propyleneglycol monololeate	0.20 g
Cremophor RH40	0.50 g
Softigen 701	0.10 g
Cremophor RH40	0.50 g
Sorbitan monocaprate	0.25 g
Cremophor RH 60	0.54 g
Span 80	0.26 g
Cremophor RH 40	0.70 g
Volpo 3	0.30 g
Crodet O40	0.68 g
Plurol Oleique	0.32 g
Crovol M-70	0.61 g
Crovol M-40	0.12 g
Crovol M-70	0.38 g
Labrafil	0.60 g
Crovol M-70	0.65 g
Imwitor 988	0.15 g
Crovol M-70	0.60 g
Linoleic acid	0.20 g
Emalex C-40	0.50 g
Gelucire 33/01	0.15 g
Glycerox L	0.73 g
Myvacet 9-45	0.27 g
Incrocas 35	0.65 g
Arlacel 186	0.12 g
Incrocas 35	0.25 g
Gelucire 44/14	0.15 g
Incrocas 35	0.83 g
Imwitor 988	0.20 g
Incrocas 35	0.31 g
Labrafil	0.11 g
Labrasol	0.83 g
Lauroglycol	0.17 g
Lauroyl carnitine	0.15 g
Imwitor 312	0.15 g
Incrocas 35	0.50 g
Myvacet 9-45	0.38 g
Incrocas-35	0.50 g

-continued

Span-20	0.15 g
Incrocas 35	0.51 g
Imwitor 988	0.22 g
Kessco PEG 300DL	0.35 g
Gelucire 50/15	0.50 g
Kessco PEG 1540DO	0.65 g
Span 80	0.12
Labrasol	0.45 g
Span-20	0.25 g
Myrj 45	0.50 g
Sorbitan monocaprylate	0.25 g
Myrj 52	0.50 g
Imwitor 308	0.20 g
Sucrose monolaurate	0.50 g
Capmul MCM	0.20 g
Nikkol Decaglyn 1-L	0.55 g
Crovol M-40	0.33 g
Nikkol Decaglyn 1-O	0.65 g
Capmul MCM	0.25 g
Nikkol DHC	0.67 g
Nikkol TMGO-5	0.17 g
Nikkol BPS-30	0.30 g
PEG-6 castor oil	0.15 g
Tween 20	0.75 g
Drewpol 6-1-O	0.15 g
Tween 20	0.34 g
Lauroglycol FCC	0.11 g
Tween 20	0.58 g
Plurol Oleique	0.21 g
Tween 80	0.67 g
Lauroglycol	0.17 g
Tagat O2	0.50 g
PGMG-03	0.05 g
Tagat L2	0.68 g
Brij 30	0.32 g
Poloxmmer 188	0.85 g
Labrafil M2125CS	0.15 g
Poloxamer 108	0.85 g
Capmul GMO-K	0.15 g
Solulan C-24	0.58 g
Lauroglycol FCC	0.21 g

C: Two Hydrophilic Surfactants and One Hydrophobic Surfactant

Cremophor EL	0.30 g
Labrasol	0.30 g
Capmul MCM	0.40 g
Cremophor RH-40	0.25 g
Labrasol	0.25 g
Capmul GMO-K	0.11 g
Cremophor RH 40	0.30 g
Tween-20	0.20 g
Nikkol Decaglyn 3-O	0.50 g
Cremophor EL-P	0.45 g
Corvol M-40	0.25 g
Sodium Docusate	0.15 g
Cremophor RH 40	0.65 g
Arlacel 186	0.15 g
Sodium dodecyl sulfate	0.10 g
Cremophor RH 40	0.50 g
Peceol	0.20 g
Sodium docusate	0.20 g
Sodium Chenodeoxycholate	0.30 g
Cremophor RH 40	0.40 g
Arlacel 186	0.30 g
Cremophor RH 40	0.41 g
Sodium taurocholate	0.26 g
Arlacel 186	0.27 g
Cremophor RH 40	0.50 g
Softigen 767	0.22 g
Arlacel 186	0.15 g
Cremophor RH 40	0.40 g
Arlacel 186	0.40 g
Tween 20	0.20 g
Cremophor RH 40	0.35 g
Capmul MCM	0.30 g
Sodium chenodeoxycholate	0.30 g
Kessco PEG 1000MO	0.30 g
Labrasol	0.30 g
Span 20	0.40 g

-continued

Polaxamer 188	0.65 g
Peceol	0.15 g
Sodium dodecyl sulfate	0.10 g
Sodium taurocholate	0.17 g
Tween 20	0.66 g
Arlacel 186	0.17 g
Sodium taurocholate	0.17 g
Kessco PEG 1000MO	0.66 g
Plurol Oleique	0.17 g
Sodium taurocholate	0.15 g
Tween 80	0.18 g
Arlacel 186	0.18 g
Thurochenodeoxycholate	0.15 g
Tween 20	0.40 g
Arlacel 186	0.15 g
Chenodeoxycholic acid	0.25 g
Incrocas-35	0.30 g
Span 20	0.20 g
Saurcocholate	0.20 g
Cremophor RH 40	0.40 g
Arlacel 186	0.20 g
Lithocholate	0.25 g
Incrocas-35	0.40 g
Myvacet 9-45	0.30 g
Tagat L2	0.45 g
Crovol A-40	0.25 g
Sodium docusate	0.15 g
Tween-20	0.30 g
Arlacel 186	0.20 g
Sodium chenodeoxycholate	0.25 g
Cremophor RH 40	0.40 g
Tween-20	0.25 g
Sodium caprate	0.25 g
Cremophor RH40	0.40 g
Lauric acid	0.20 g
Incrocas-35	0.30 g
D: One Hydrophilic and Two Hydrophobic Surfactants	
Cremophor RH 40	0.50 g
Labrafil M2125CS	0.27 g
Crovol M-40	0.28 g
Cremophor RH 40	1.53 g
Arlacel 186	0.38 g
Peceol	0.38 g
HPB beta cyclodextrin	0.38 g
Cremophor RH 40	0.55 g
Labrafil M2125 CS	0.34 g
Span 80	0.2 g
Cremophor RH 40	0.50 g
Labrafil M2125 Cs	0.27 g
Crovol M-40	0.28 g
E: Two Hydrophilic and Two Hydrophobic Surfactants	
Polaxamer 108	0.45 g
Span 20	0.25 g
Sodium docusate	0.15 g
Ethyl oleate	0.15 g
Softigen 767	0.45 g
Imwitor 742	0.25 g
Sodium docusate	0.15 g
Ethyl oleate	0.15 g

Example 5

Compositions with Hydrophilic Therapeutic Agent

Typical compositions having a hydrophilic therapeutic agent can have components and concentrations in the following exemplary, but not limiting ranges, in percent by weight unless otherwise indicated:

absorption enhancing composition	10–100%
enzyme inhibitor (e.g., aprotinin)	0–10%
solubilizer (e.g., propylene glycol)	0–60%
bufferant	0–50 mM
hydrophilic polymer (e.g., HPMC)	0–20% w/w
other additives	0–50%

If formulated as an aqueous dosage form, a typical amount of water would be about 250 mL, or any other convenient amount.

Typical hydrophilic therapeutic agents and amounts in mg or IU/mL or G:

alendronate Sodium	5–50 mg
etidronate disodium	200–400 mg
pamidronate disodium	30–90 mg
aztreonam	20–500 mg
valacylcovir	250–1000 mg
gancyclovir	250–500 mg
famcyclovir	125–200 mg
pericyclovir	125–1000 mg
pyridostigmine	60 mg
cromalyn sodium	0.1–2 mg
nedocromil sodium	0.1–2 mg
metformin hydrochloride	500–850 mg
acarbose	50–100 mg
amphotericin B	50–200 mg
octreotide acetate	0.1 to 1 mg
cefoxitin sodium	200–1000 mg
corticotropin:	25–1000 IU
sodium heparin	20–5000 IU
desmopressin acetate (DVAP)	0.1–1 mg
vasopressin	5–100 IU
salmon calcitonin	500 IU
insulin	140 IU
erythropoietin	14,000 mg
porcine somatotropin	50 mg
recombinant growth hormone	30 IU
oligonucleotide	1–500 mg

Of course, the amounts listed are chosen to be therapeutically effective amounts, but the invention is not limited thereby.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed and desired to be secured by United States Letters Patent is:

1. A pharmaceutical system for enhanced absorption of a hydrophilic therapeutic agent, the system consisting essentially of:

(a) a dosage form of an absorption enhancing composition, the composition comprising:

(i) at least one hydrophilic surfactant selected from the group consisting of ionized ionizable surfactants, non-ionic hydrophilic surfactants having an HLB value greater than or equal to about 10, and combinations thereof, and

(ii) at least one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid

monoesters, lower alcohol fatty acid diesters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carnitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof,

wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent at 100x dilution, the composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm; and

(b) a therapeutically effective amount of a hydrophilic therapeutic agent, wherein the pharmaceutical system is free of triglycerides.

2. The pharmaceutical system of claim 1, wherein the hydrophilic surfactant comprises at least one ionized ionizable surfactant.

3. The pharmaceutical system of claim 2, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of bile acids and salts, analogues, and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-acetylated tartaric esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides; succinylated monoglycerides; citric acid esters of mono- and diglycerides; and mixtures thereof.

4. The pharmaceutical system of claim 2, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, lithocholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, tetraacetyl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

5. The pharmaceutical system of claim 2, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholate, taurocholate, glycocholate, deoxycholate, chenodeoxycholate, lithocholate, ursodeoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

6. The pharmaceutical system of claim 2, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, chenodeoxycholate, lithocholate, ursodeoxycholate, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

7. The pharmaceutical system of claim 1, wherein the hydrophilic surfactant comprises at least one non-ionic hydrophilic surfactant having an HLB value greater than or equal to about 10.

8. The pharmaceutical system of claim 7, wherein the non-ionic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

9. The pharmaceutical system of claim 7, wherein the non-ionic hydrophilic surfactant is selected from the group consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils; and mixtures thereof.

10. The pharmaceutical system of claim 9, wherein the non-ionic hydrophilic surfactant is the reaction product of a polyol and a monoglyceride, diglyceride, triglyceride, or a mixture thereof.

11. The pharmaceutical system of claim 10, wherein the reaction product comprises a transesterification product.

12. The pharmaceutical system of claim 10, wherein the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

13. The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is selected from the group consisting of PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35

castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG -8 caprate/caprylate diglycerides, polyglyceryl-10 laurate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, and combinations thereof.

14. The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is selected from the group consisting of PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, polyglyceryl-10 laurate, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG-8 caprate/caprylate diglycerides, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, sucrose monostearate, sucrose monolaurate, a poloxamer, and combinations thereof.

15. The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG-8 caprate/caprylate diglycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, a poloxamer, and combinations thereof.

16. The pharmaceutical system of claim 1, wherein the composition comprises at least two hydrophilic surfactants.

17. The pharmaceutical system of claim 1, wherein the hydrophobic surfactant comprises an un-ionized ionizable surfactant.

18. The pharmaceutical system of claim 17, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of bile acids and analogues and derivatives thereof; carnitine fatty acid esters; alkylsulfates; fatty acids; acyl lactylates; mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides; succinylated monoglycerides; citric acid esters of mono- and diglycerides; and mixtures thereof.

19. The pharmaceutical system of claim 17 wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, glycodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid, lithocholic acid, tauroursodeoxycholic acid, glycoursodeoxycholic acid, cholylsarcosine, N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic acid, stearic acid, lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

20. The pharmaceutical system of claim 17, wherein the un-ionized ionizable surfactant is the unionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid, cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric acid, oleic acid, lauryl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

21. The pharmaceutical system of claim 17, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurocholic acid, caprylic acid, capric acid, oleic acid, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

22. The pharmaceutical system of claim 1, wherein the hydrophobic surfactant comprises at least one surfactant having an HLB value less than about 10.

23. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono- and diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils; and mixtures thereof.

24. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is selected from the group consisting of fatty acids; bile acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono- and diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils; and mixtures thereof.

25. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is selected from the group consisting of bile acids; lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono- and diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof.

26. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is a glycerol fatty acid ester selected

from the group consisting of glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, or a mixture thereof.

27. The pharmaceutical system of claim 26, wherein the glycerol fatty acid ester is selected from the group consisting of glycerol fatty acid monoesters, glycerol fatty acid diesters, and mixtures thereof.

28. The pharmaceutical system of claim 27, wherein the fatty acid of the glycerol fatty acid ester is a C_6 to C_{22} fatty acid or a mixture thereof.

29. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is a reaction product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils.

30. The pharmaceutical system of claim 29, wherein the reaction product is a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils.

31. The pharmaceutical system of claim 29, wherein the polyol is polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

32. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{22} fatty acid; monoglycerides of a C_6 to C_{22} fatty acid; acetylated monoglycerides of C_6 to C_{22} fatty acid; diglycerides of C_6 to C_{22} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid; lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

33. The pharmaceutical system of claim 22, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid, PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG-3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; mono, di, tri, tetra esters vegetable oil and sorbitol; pentacrythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{22} fatty acid; monoglycerides of a C_6 to C_{22} fatty acid; acetylated monoglycerides of C_6 to C_{22} fatty acid; diglycerides of C_6 to C_{22} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan monooleate; sorbitan monostearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid; lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

34. The pharmaceutical system of claim 1, wherein each of the at least two surfactants is selected from the group consisting of sodium lauryl sulfate, oleic acid, linoleic acid, monoolein, deoxycholate, taurodeoxycholate, glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20, sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether; polyoxyethylene sorbitan esters, p-t-octylphenoxypolyoxyethylene, N-lauryl-β-D-maltopyranoside, and 1-dodecylazacycloheptane-2-azone, and is present in an amount of greater than 10% by weight, based on the total weight of the pharmaceutical system.

35. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is a drug, a vitamin, a nutritional supplement, a cosmeceutical, a diagnostic agent, or a mixture thereof.

36. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent has an apparent water solubility of at least about 1 mg/mL.

37. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is a hydrophilic drug, a cytokine, a peptidomimetic, a peptide, a protein, a toxoid, a serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of genetic material, a nucleic acid, or a mixture thereof.

38. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is selected from the hydrophilic members of the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic, sedatives, hypnotics, neuroleptics, β-Blockers, cardiac inotropic agents, corticosteriods, diuretics, anti-parkinsonian agents, gastrointestinal agents, histamine H,-receptor antagonists, keratolytics, lipid regulating agents, muscle relaxants, anti-anginal agents, nutritional agents, analgesics, sex hormones, stimulants, cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides, genetic material, nucleic acids, and mixtures thereof.

39. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride; ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human); antihemophilic factor

(porcine); antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladona; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; cephapirin sodium; cholera vaccine; chrionic gonadotropin; cidofovir; cisplatin; cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate; colistimethate sodium; colistin sulfate; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin; diatrizoate megluamine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin; dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin; editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famiciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; measles virus vaccine; meningococcal vaccine; menotropins; mephenzolate bromide; mesalmine; methanamine; methotrexate; methscopolamine; metformin hydrochloride; metroprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; norfloxacin; octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine; pefloxacin; pentamindine isethionate; pentostatin; pentoxifylline; periciclovir; pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate; plague vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine; solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase; streptozocin; suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trandolapril; trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan; variella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium bromide; vinblastin; vincristine; vinorelbine; vitamin B12; warfarin sodium; yellow fever vaccine; zalcitabine; zanamavir; zolandronate; and zidovudine.

40. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; acyclovir; atracurium besylate; alendronate; alglucerase; amantadine hydrochloride; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant; azithromycin; calcitonin human; calcitonin salmon; capecitabine; cefazolin sodium; cefonicid sodium; cefoperazone; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuiroxime axetil; cephalexin; chrionic gonadotropin; cidofovir; cladribine; clindamycin and clindamycin derivatives; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; desmopressin; didanosine; dirithromycin; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; farmiciclovir; fluradabine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-Bovine; gentamycin; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; lamivudine; leucovorin calcium; leuprolide acetate; lincomycin and lincomycin derivatives; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; pancuronium bromide; pentamindine isethionate; pentagastrin; physostigmine salicylate; poliovirus vaccine live (OPV); pyridostigmine bromide; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; somatostatin; spectinomycin; stavudine; streptokinase; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trimetrexate gluconate; trospectinomycin; tumor necrosis factor; typhoid vaccine live; urokinase; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; vinblastin; vincristine; vinorelbine; warfarin sodium; zalcitabine; zanamavir; and zidovudine.

41. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin human; calcitonin salmon; ceftriaxone; cefuroxime axetil; chrionic gonadotropin; cromalyn sodium; daltaperin sodium; danaproid; desmopressin; didanosine; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-Bovine; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine interferon alpha; interferon beta; leuprolide acetate; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; residronate; rimantadine hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis factor; typhoid vaccine live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine; zanamavir and zidovudine.

42. The pharmaceutical system of claim 1, wherein the composition further includes at least one pharmaceutical additive selected from the group consisting of an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a suspending agent, a binder, a filler, a plasticizer, a lubricant, an enzyme inhibiting agent, and combinations thereof.

43. The pharmaceutical system of claim 42, wherein the composition includes an enzyme inhibiting agent present in an amount sufficient to at least partially inhibit enzymatic degradation of the hydrophilic therapeutic agent.

44. The pharmaceutical system of claim 43, wherein the enzyme inhibiting agent is P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, an amino acid, a modified amino acid, a peptide, a modified peptide, a polypeptide protease inhibitor, a complexing agent, a mucoadhesive polymer, a polymer-inhibitor conjugate, or a mixture thereof.

45. The pharmaceutical system of claim 44, wherein the enzyme inhibiting agent is selected from the group consisting of P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, aminoboronic acid derivatives, n-acetylcysteine, bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin, chymostatin, elastatin, bestatin, hosphoramindon, puromycin, cytochalasin potatocarboxy peptidase inhibitor, amastatin, protinin, Bowman-Birk inhibitor, soybean trypsin inhibitor, chicken egg white trypsin inhibitor, chicken ovoinhibitor, human pancreatic trypsin inhibitor, EDTA, EGTA, 1,10-phenanthroline, hydroxychinoline, polyacrylate derivatives, chitosan, cellulosics, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor, and mixtures thereof.

46. The pharmaceutical system of claim 1, wherein the composition further comprises a pharmaceutically acceptable acid.

47. The pharmaceutical system of claim 46, wherein the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, carbonic acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and mixtures thereof.

48. The pharmaceutical system of claim 1, wherein the composition further comprises a pharmaceutically acceptable base.

49. The pharmaceutical system of claim 48, wherein the base is an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid, or a mixture thereof.

50. The pharmaceutical system of claim 1, wherein the aqueous dispersion formed by the composition upon contact with an aqueous medium has an average particle size of less than about 200 nm upon mixing with an aqueous diluent.

51. The pharmaceutical system of claim 50, wherein the average particle size is less than about 100 nm.

52. The pharmaceutical system of claim 50, wherein the average particle size is less than about 50 nm.

53. The pharmaceutical system of claim 1, wherein the system is free of polyethylene glycol diesters.

54. The pharmaceutical system of claim 1, wherein the dosage form is free of water.

55. The pharmaceutical system of claim 1 in the form of a preconcentrate in a liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate.

56. The pharmaceutical system of claim 1, wherein the dosage form of the composition is processed by balling, lyophilization, encapsulation, extruding, compression, melting, molding, spraying, spray congealing, coating, comminution, mixing, cryopelletization, spheronization, homogenization, sonication, granulation, or a combination thereof.

57. The pharmaceutical system of claim 1, wherein the dosage form of the composition is a pill, capsule, caplet, tablet, granule, pellet, bead or powder.

58. The pharmaceutical system of claim 1, wherein the dosage form of the composition is a starch capsule, a cellulosic capsule, a hard gelatin capsule or a soft gelatin capsule.

59. The pharmaceutical system of claim 1, wherein the dosage form is formulated for immediate release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

60. The pharmaceutical system of claim 57, coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

61. The pharmaceutical system of claim 60, wherein the coating is comprised of a material selected from the group consisting of shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof.

62. The pharmaceutical system of claim 60, herein the coating is comprised of a material selected from the group consisting of acrylic acid and methacrylic acid resins, cellulose acetate phthalate, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, and mixtures thereof.

63. The pharmaceutical system of claim 60, wherein the coating is comprised of a material selected from the group consisting of acrylic acid and methacrylic acid resins, cellulose acetate phthalate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, and mixtures thereof.

64. The pharmaceutical system of claim 1, wherein the dosage form of the composition is a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup or elixir.

65. The pharmaceutical system of claim 1, wherein the dosage form is a multiparticulate carrier coated onto a substrate with the composition.

66. The pharmaceutical system of claim 65, wherein the substrate is a particle, a granule, a pellet or a bead, and is formed of the therapeutic agent, a pharmaceutically acceptable material, or a mixture thereof.

67. The pharmaceutical system of claim 65, wherein the multiparticulate carrier is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

68. The pharmaceutical system of claim 65, wherein the dosage form is further processed by encapsulation, compression, extrusion, molding, spheronization or cryopelletization.

69. The pharmaceutical system of claim 65, wherein the dosage form is further processed to form a starch capsule, a cellulosic capsule, a hard gelatin capsule, or a soft gelatin capsule.

70. The pharmaceutical system of claim 69, wherein the capsule is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

71. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is present in the dosage form.

72. The pharmaceutical system of claim 71, wherein the hydrophilic therapeutic agent is solubilized in the composition, suspended in the composition, or partially solubilized and partially suspended in the composition.

73. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic agent is present in a second dosage form separate from the dosage form containing the absorption enhancing composition.

74. The pharmaceutical system of claim 1, wherein the dosage form of the composition is formulated for oral, mucosal, nasal, pulmonary, vaginal, transmembrane, buccal or rectal administration.

75. The pharmaceutical system of claim 73, wherein the dosage form of the hydrophilic therapeutic agent is formulated for oral, mucosal, nasal, pulmonary, vaginal, transmembrane, buccal or rectal administration.

76. A pharmaceutical system for enhanced absorption of a hydrophilic therapeutic agent, the system consisting essentially of:

(a) a dosage form of an absorption enhancing composition, the composition comprising:

(i) at least one hydrophilic surfactant selected from the group consisting of ionized surfactants, non-ionic hydrophilic surfactants having an HLB value greater than or equal to about 10, and combinations thereof,

(ii) at least one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid monoesters, lower alcohol fatty acid diesters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carnitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof, wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent at 100× dilution, the composition forms an aqueous dispersion having an average particle size of less than about 200 nm, and

(iii) at least one solubilizer; and

(b) a therapeutically effective amount of a hydrophilic therapeutic agent, wherein the pharmaceutical system is free of triglycerides.

77. The pharmaceutical system of claim 76, wherein the hydrophilic surfactant comprises at least one ionized ionizable surfactant.

78. The pharmaceutical system of claim 77, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of bile acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides; succinylated monoglycerides; citric acid esters of mono- and diglycerides; and mixtures thereof.

79. The pharmaceutical system of claim 77, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxychorate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, lithocholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, tetraacetyl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

80. The pharmaceutical system of claim 77, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholate, taurocholate, glycocholate, deoxycholate, chenodeoxycholate, lithocholate, ursodeoxycholate, taurodeoxycholate,

glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

81. The pharmaceutical system of claim 77, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, chenodeoxycholate, lithocholate, ursodeoxycholate, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

82. The pharmaceutical system of claim 76, wherein the hydrophilic surfactant comprises at least one non-ionic hydrophilic surfactant having an HLB value greater than or equal to about 10.

83. The pharmaceutical system of claim 82, wherein the non-ionic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

84. The pharmaceutical system of claim 82, wherein the non-ionic hydrophilic surfactant is selected from the group consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

85. The pharmaceutical system of claim 84, wherein the non-ionic hydrophilic surfactant is the reaction product of a polyol and a monoglyceride, diglyceride, triglyceride, or a mixture thereof.

86. The pharmaceutical system of claim 85, wherein the reaction product comprises the transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

87. The pharmaceutical system of claim 85, wherein the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

88. The pharmaceutical system of claim 82, wherein the hydrophilic surfactant is selected from the group consisting of PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEGG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG-8 caprate/caprylate diglycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, aid combinations thereof.

89. The pharmaceutical system of claim 82, wherein the hydrophilic surfactant is selected from the group consisting of PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, polyglyceryl-10 laurate, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG-8 caprate/caprylate diglycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, and combinations thereof.

90. The pharmaceutical system of claim 82, wherein the hydrophilic surfactant is selected from the group consisting of PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate monoglycerides, PEG-6 caprate/caprylate diglycerides, PEG-8 caprate/caprylate monoglycerides, PEG-8 caprate/caprylate diglycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, and combinations thereof.

91. The pharmaceutical system of claim 76, wherein the composition comprises at least two hydrophilic surfactants.

92. The pharmaceutical system of claim 76, wherein the hydrophobic surfactant comprises an un-ionized ionizable surfactant.

93. The pharmaceutical system of claim 92, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of bile acids and analogues and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid esters; alkylsulfates; fatty acids; acyl lactylates; mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides; succinylated monoglycerides; citric acid esters of mono- and diglycerides; and mixtures thereof.

94. The pharmaceutical system of claim 92, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated

tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, glycodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid, lithocholic acid, tauroursodeoxycholic acid, glycoursodeoxycholic acid, cholylsarcosine, N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic acid, stearic acid, lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

95. The pharmaceutical system of claim 92, wherein the un-ionized ionizable surfactant is the unionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid, cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric acid, oleic acid, lauryl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

96. The pharmaceutical system of claim 92, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurocholic acid, caprylic acid, capric acid, oleic acid, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

97. The pharmaceutical system of claim 92 wherein the hydrophobic surfactant comprises at least one surfactant having an HLB value less than about 10.

98. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono- and diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

99. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is selected from the group consisting of fatty acids; bile acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono- and diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

100. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is selected from the group consisting of bile acids; lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono- and diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof.

101. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is a glycerol fatty acid ester selected from the group consisting of glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, and mixtures thereof.

102. The pharmaceutical system of claim 97, wherein the glycerol fatty acid ester is selected from the group consisting of glycerol fatty acid monoesters, glycerol fatty acid diesters, and mixtures thereof.

103. The pharmaceutical system of claim 102, wherein the fatty acid of the glycerol fatty acid ester is a C_6 to C_{22} fatty acid or a mixture thereof.

104. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is a reaction product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

105. The pharmaceutical system of claim 104, wherein the reaction product is a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

106. The pharmaceutical system of claim 105, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{22} fatty acid; monoglycerides of a C_6 to C_{22} fatty acid; acetylated monoglycerides of C_6 to C_{22} fatty acid; diglycerides of C_6 to C_{22} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; PEG 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose.

107. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 24 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PETG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{22} fatty acid; monoglycerides of a C_6 to C_{22} fatty acid; acetylated monoglycerides of C_6 to C_{22} fatty acid; diglycerides or C_6 to C_{22} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol: PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaturate; sorbitan monopalmitate; sorbitan monooleate; sorbitan monostearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PFG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers; cholic acid; ursodeoxycholic acid; glycocliolic acid; taurocliolic acid; lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

108. The pharmaceutical system of claim 97, wherein the hydrophobic surfactant is selected from the group consisting of oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid; lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

109. The pharmaceutical system of claim 76, wherein the hydrophobic and hydrophilic surfactants are selected from the hydrophobic and hydrophilic members, respectively, of the group consisting of sodium lauryl sulfate, oleic acid, linoleic acid, monoolein, lecithin, lysolecithin, deoxycholate, taurodeoxycholate, glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20, sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether, polyoxyethylene sorbitan esters, p-t-octylphenoxypolyoxyethylene, N-lauryl-β-D-maltopyranoside, 1-dodecylazacycloheptane-2-azone, and phospholipids, and are each present in an amount of greater than 10% by weight, based on the total weight of the pharmaceutical system.

110. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is a drug, a vitamin, a nutritional supplement, a cosmeceutical, a diagnostic agent, or a mixture thereof.

111. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent has an apparent water solubility of at least about 1 mg/mL.

112. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is a hydrophilic drug, a cytokine, a peptidomimetic, a peptide, a protein, a toxoid, a serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of genetic material, a nucleic acid, or a mixture thereof.

113. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is selected from the hydrophilic members of the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic, sedatives, hypnotics, neuroleptics, β-Blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastrointestinal agents, histamine H_1-receptor antagonists, keratolytics, lipid regulating agents, muscle relaxants, anti-anginal agents, nutritional agents, analgesics, sex hormones, stimulants, cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides, genetic material, nucleic acids, and mixtures thereof.

114. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride; ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladona; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; cephapirin sodium; cholera vaccine; chrionic gonadotropin; cidofovir; cisplatin; cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate; colistimethate sodium; colistin sulfate; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin; diatrizoate megluamine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin; dopamine hydrochloride; domase alpha; doxacurium chloride; doxorubicin; editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famiciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor, granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; measles virus vaccine; meningococcal vaccine;

menotropins; mephenzolate bromide; mesalmine; methanamine; methotrexate; methscopolamine; metformin hydrochloride; metroprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; norfloxacin; octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine; pefloxacin; pentamindine isethionate; pentostatin; pentoxifylline; periciclovir; pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate; plague vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine; solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase; streptozocin; suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trandolapril; trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan; varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium bromide; vinblastin; vincristine; vinorelbine; vitamin B12; warfarin sodium; yellow fever vaccine; zalcitabine; zanamavir; zolandronate; and zidovudine.

115. The pharmaceutical system of claim **76**, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; acyclovir; atracurium besylate; alendronate; alglucerase; amantadine hydrochloride; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant; azithromycin; calcitonin human; calcitonin salmon; capecitabine; cefazolin sodium; cefonicid sodium; cefoperazone; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; chrionic gonadotropin; cidofovir; cladribine; clindamycin and clindamycin derivatives; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; desmopressin; didanosine; dirithromycin; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; fludarabine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-Bovine; gentamycin; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; lamivudine; leucovorin calcium; leuprolide acetate; lincomycin and lincomycin derivatives; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; pancuronium bromide; pentamindine isethionate; pentagastrin; physostigmine salicylate; poliovirus vaccine live (OPV); pyridostigmine bromide; residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; somatostatin; spectinomycin; stavudine; streptokinase; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trimetrexate gluconate; trospectinomycin; tumor necrosis factor; typhoid vaccine live; urokinase; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; vinblastin; vincristine; vinorelbine; warfarin sodium; zalcitabine; zanamavir; and zidovudine.

116. The pharmaceutical system of claim **76**, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin human; calcitonin salmon; ceftriaxone; cefuiroxime axetil; chrionic gonadotropin; cromalyn sodium; daltaperin sodium; danaproid; desmopressin; didanosine; editronate disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-recombinant human; growth hormone-Bovine; glucagon; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine interferon alpha; interferon beta; leuprolide acetate; metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; residronate; rimantadine hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis factor; typhoid vaccine live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine; zanamavir and zidovudine.

117. The pharmaceutical system of claim **76**, wherein the solubilizer is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

118. The pharmaceutical system of claim **76**, wherein the composition further comprises includes at least one pharmaceutical additive selected from the group consisting of an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a suspending agent, a binder, a filler, a plasticizer, a lubricant, an enzyme inhibiting agent, and combinations thereof.

119. The pharmaceutical system of claim **118**, wherein the composition includes an enzyme inhibiting agent present in an amount sufficient to at least partially inhibit enzymatic degradation of the hydrophilic therapeutic agent.

120. The pharmaceutical system of claim **119**, wherein the enzyme inhibiting agent is P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, an amino acid, a modified amino acid, a peptide, a modified peptide, a polypeptide protease inhibitor, a complexing agent, a mucoadhesive polymer, a polymer-inhibitor conjugate, or a mixture thereof.

121. The pharmaceutical system of claim **119**, wherein the enzyme inhibiting agent is selected from the group consisting of P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, aminoboronic acid derivatives, n-acetylcysteine, bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin, chymostatin, elastatin, bestatin, hospboramindon, puromycin, cytochalasin potatocarboxy peptidase inhibitor, amastatin, protinin, Bowman-Birk inhibitor, soybean trypsin inhibitor, chicken egg white trypsin inhibitor, chicken ovoinhibitor, human pancreatic trypsin inhibitor, EDTA, EGTA, 1,10-phenanthroline, hydroxychinoline, polyacrylate derivatives, chitosan, cellulosics, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor, and mixtures thereof.

122. The pharmaceutical system of claim 76, wherein the composition further comprises a pharmaceutically acceptable acid.

123. The pharmaceutical system of claim 122, wherein the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, carbonic acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and mixtures thereof.

124. The pharmaceutical system of claim 76, wherein the composition further comprises a pharmaceutically acceptable base.

125. The pharmaceutical system of claim 124, wherein the base is an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid, or a mixture thereof.

126. The pharmaceutical system of claim 76, wherein the average particle size of the aqueous dispersion formed upon mixing the composition with an aqueous diluent is less than about 100 nm.

127. The pharmaceutical system of claim 126, wherein the average particle size is less than about 50 nm.

128. The pharmaceutical system of claim 76, wherein the composition forms a substantially optically clear aqueous dispersion having an absorbance of less than about 0.3 at 400 upon mixing with an aqueous diluent at 100× dilution.

129. The pharmaceutical system of claim 76, wherein the system is free of polyethylene glycol diesters.

130. The pharmaceutical system of claim 76, wherein the system is free of cholesterol.

131. The pharmaceutical system of claim 76, wherein the dosage form is free of water.

132. The pharmaceutical system of claim 76 in the form of a preconcentrate in a liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate.

133. The pharmaceutical system of claim 76, wherein the dosage form of the composition is processed by balling, lyophilization, encapsulation, extruding, compression, melting, molding, spraying, spray congealing, coating, comminution, mixing, cryopelletization, spheronization, homogenization, sonication, granulation, or a combination thereof.

134. The pharmaceutical system of claim 76, wherein the dosage form of the composition is a pill, capsule, caplet, tablet, granule, pellet, bead or powder.

135. The pharmaceutical system of claim 76, wherein the dosage form of the composition is a starch capsule, a cellulosic capsule, a hard gelatin capsule or a soft gelatin capsule.

136. The pharmaceutical system of claim 76, wherein the dosage form is formulated for immediate release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

137. The pharmaceutical system of claim 134, which further comprises at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

138. The pharmaceutical system of claim 137, wherein the coating is comprised of a material selected from the group consisting of shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof.

139. The pharmaceutical system of claim 137, wherein the coating is formed of a material selected from the group consisting of acrylic acid and methacrylic acid resins, cellulose acetate phthalate, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, and mixtures thereof.

140. The pharmaceutical system of claim 137, wherein the coating is formed of a material selected from the group consisting of acrylic acid and methacrylic acid resins, cellulose acetate phthalate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, and mixtures thereof.

141. The pharmaceutical system of claim 76, wherein the dosage form of the composition is a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup or elixir.

142. The pharmaceutical system of claim 76, wherein the dosage form is a multiparticulate carrier coated onto a substrate with the composition.

143. The pharmaceutical system of claim 142, wherein the substrate is a particle, a granule, a pellet or a bead, and is formed of the therapeutic agent, a pharmaceutically acceptable material, or a mixture thereof.

144. The pharmaceutical system of claim 142, wherein the multiparticulate carrier is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

145. The pharmaceutical system of claim 142, wherein the dosage form is further processed by encapsulation, compression, extrusion, molding, spheronization or cryopelletization.

146. The pharmaceutical system of claim 142, wherein the dosage form is further processed to form a starch capsule, a cellulosic capsule, a hard gelatin capsule, or a soft gelatin capsule.

147. The pharmaceutical system of claim 146, wherein the capsule is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

148. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is present in the dosage form.

149. The pharmaceutical system of claim 147, wherein the hydrophilic therapeutic agent is solubilized in the composition, suspended in the composition, or partially solubilized and partially suspended in the composition.

150. The pharmaceutical system of claim 76, wherein the hydrophilic therapeutic agent is present in a second dosage form separate from the dosage form containing the absorption enhancing composition.

151. The pharmaceutical system of claim 76, wherein the dosage form of the composition is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

152. The pharmaceutical system of claim 151, wherein the dosage form of the hydrophilic therapeutic agent is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

153. An absorption enhancing composition for co-administration to a patient with a hydrophilic therapeutic agent, the composition consisting essentially of an effective amount of am absorption enhancer comprising at least one hydrophilic surfactant selected from the group consisting of ionized surfactants, non-ionic hydrophilic surfactants having an HLB value greater than or equal to 10, mid combinations thereof, and at least cast one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid monoesters, lower alcohol fatty acid diesters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, soibitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction prodeucts of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carmitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof, wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent the composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm, the absorption enhancing composition being free of triglycerides.

154. The composition of claim 153, wherein the effective amount is an amount sufficient to increase the rate, the extent, or both the rate and extent, of bioabsorption of a hydrophilic therapeutic agent, when the composition and the hydrophilic therapeutic agent are administered to a patient.

155. The composition of claim 153, wherein the effective amount is an amount sufficient to improve the consistency of the rate, the extent, or both the rate and extent, of bioabsorption of a hydrophilic therapeutic agent, when the composition and the hydrophilic therapeutic agent are administered to a patient.

156. A method of controlling the rate, the extent, or both the rate ant extent of bioabsorption of a hydrophilic therapeutic agent administered to a patient, the method comprising:

(a) providing a dosage form of an absorption enhancing composition, the composition consisting essentially of at least one hydrophilic surfactant selected from the group consisting of ionized surfactants, non-ionic hydrophilic surfactants having an HLB value greater than or equal to 10, and combinations thereof, and at least one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, glycerol fatty acid diesters, lower alcohol fatty acid monoesters, lower alcohol fatty acid diesters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carnitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerdied, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof, wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent the composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm, and wherein the composition is free of triglycerides;

(b) providing a hydrophilic therapeutic agent; and

(c) administering the dosage form of the absorption enhancing composition and the hydrophilic therapeutic agent to the patient.

157. The method of claim 156, wherein the hydrophilic therapeutic agent is contained in the dosage form of the absorption enhancing composition.

158. The method of claim 157, wherein the hydrophilic therapeutic agent is solubilized, suspended, or partially solubilized and partially suspended, in the dosage form of the absorption enhancing composition.

159. The method of claim 156, wherein the hydrophilic therapeutic agent is provided in a second dosage form separate from the dosage form containing the absorption enhancing composition.

160. The method of claim 159, wherein the step of administering comprises administering the dosage form of the absorption enhancing composition and co-administering the dosage form of the hydrophilic therapeutic agent.

161. The method of claim 156, wherein the dosage form of the absorption enhancing composition is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

162. The method of claim 159, wherein the dosage form of the hydrophilic therapeutic agent is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

163. The method of claim 156, wherein the patient is a mammal.

164. The method of claim 156, wherein the patient is a human.

165. A pharmaceutical system for enhanced absorption of a hydrophilic therapeutic agent in the form of a diluted preconcentrate, the system consisting essentially of:

(a) a dosage form of an absorption enhancing composition, the composition comprising:

(i) at least one hydrophilic surfactant selected from the group consisting of ionized ionizable surfactants,

non-ionic hydrophilic surfactants having an HLB value greater than or equal to 10, and combinations thereof,

(ii) at least one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid monoesters, lower alcohol fatty acid diestes, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carnitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartaric acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof, wherein the hydrophilic aid hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent at 100x dilution, the composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm,

(iii) a liquid diluent; and

(b) a therapeutically effective amount of a hydrophilic therapeutic agent;

wherein the pharmaceutical system is free of triglycerides.

166. A pharmaceutical system for enhancing absorption, or a hydrophilic therapeutic agent in the form of a diluted preconcentrate, the system consisting essentially of:

(a) a dosage form of an absorption enhancing composition, the composition comprising:

(i) at least one hydrophilic surfactant selected from the group consisting of ionized ionizable surfactants, non-ionic hydrophilic surfactants having an HLB value greater than or equal to 10, and combinations thereof,

(ii) at least one hydrophobic surfactant selected from the group consisting of hydrophobic (a) alcohols, polyoxyethylene alkylethers, bile acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid monoesters, lower alcohol fatty acid diesters, polyethylene glycol fatty acid monoesters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of mono- and diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, and hydrogenated vegetable oils, and hydrophobic, un-ionized (b) fatty acids, carnitine fatty acid esters, alkylsulfates, acyl lactylates, mono-acetylated tartarie acid esters of mono- and diglycerides, diacetylated tartaric acid esters of mono- and diglycerides, succinylated monoglycerides, citric acid esters of mono- and diglycerides, and mixtures thereof, wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent at 100x dilution, the composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm, wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon mixing with an aqueous diluent at 100x dilution, The composition forms a clear aqueous dispersion having an absorbance of less than about 0.3 at 400 nm,

(iii) at least one solubilizer, and

(iv) a liquid diluent; and

(b) a therapeutically effective amount of a hydrophilic therapeutic agent;

wherein the pharmaceutical system is free of triglycerides.

167. The pharmaceutical system of claim 165, wherein the therapeutic agent is provided to the system in the liquid diluent.

168. The pharmaceutical system of claim 165, further comprising an amount of an enzyme inhibiting agent sufficient to at least partially inhibit enzymatic degradation of the hydrophilic therapeutic agent, the enzyme inhibiting agent being solubilized, suspended, or partially solubilized and partially suspended, in the aqueous medium.

169. The pharmaceutical system of claim 166, wherein the therapeutic agent is provided to the system in the liquid diluent.

170. The pharmaceutical system of claim 166, further comprising an amount of an enzyme inhibiting agent sufficient to at least partially inhibit enzymatic degradation of the hydrophilic therapeutic agent, the enzyme inhibiting agent being solubilized, suspended, or partially solubilized and partially suspended, in the aqueous medium.

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[45] Date of Patent: Jul. 1, 1997

[54] **PHARMACEUTICAL COMPOSITION COMPRISING A GLUCOSIDASE AND/OR AMYLASE INHIBITOR, AND A LIPASE INHIBITOR**

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[58] **Field of Search** 514/12, 13, 54, 514/909

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[57] **ABSTRACT**

A pharmaceutical composition containing a glucosidase and/or amylase inhibitor and a lipase inhibitor as active substances and usual pharmaceutical carriers.

21 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION COMPRISING A GLUCOSIDASE AND/OR AMYLASE INHIBITOR, AND A LIPASE INHIBITOR

BRIEF SUMMARY OF THE INVENTION

The invention relates to pharmaceutical compositions containing an effective amount of at least one but no more than two glucosidase and/or amylase inhibitors and a lipase inhibitor as active substances; and the usual pharmaceutical carriers.

In another aspect, the invention relates to the use of at least one but no more than two glucosidase and/or amylase inhibitors for the combined simultaneous, separate or chronologically spaced use with a lipase inhibitor in the treatment of obesity.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that such preparations can be used for the treatment of obesity.

Accordingly, the invention is also concerned with the use of at least one but no more than two glucosidase and/or amylase inhibitors for the combined simultaneous, separate or chronologically spaced use with a lipase inhibitor in the treatment of obesity.

Further, the invention is concerned with the use of at least one but no more than two glucosidase and/or amylase inhibitors in the manufacture of pharmaceutical compositions for the combined use with a lipase inhibitor in the treatment of obesity.

Examples of known glucosidase and/or amylase inhibitors which can be used, in accordance with the invention are:

O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)O-α-D-glucopyranosyl-(1→4)-D-glucose, also known as acarbose;

2(S),3(R) ,4(S),5(S)-tetrahydroxy-N-[2-hydroxy-1-(hydroxymethyl)-ethyl]-5-(hydroxymethyl)-1(S)-cyclohexamine, also known as voglibose;

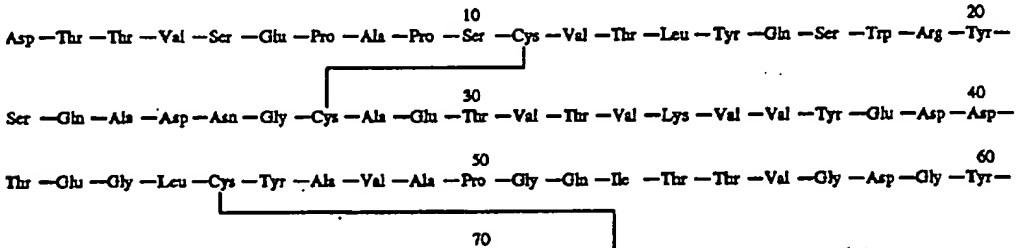
1,5-dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol, also known as miglitol;

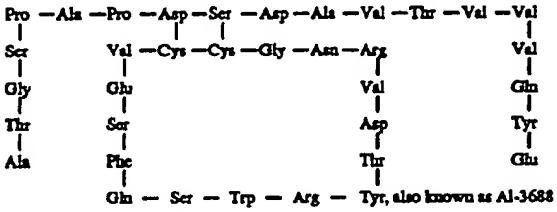
1,5-dideoxy-1,5-[2-(4-ethoxycarbonylphenoxy)ethylimino]-D-glucitol, also known as emiglitate;

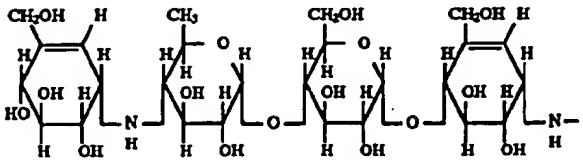
2,6-dideoxy-2,6-imino-7-(β-D-glucopyranosyl)-D-glycero-L-guloheptitol, also known as MDL-25637;

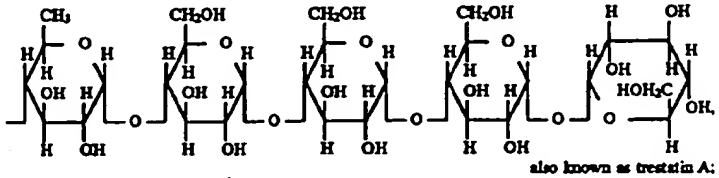
1,5-dideoxy-1,5-(6-deoxy-1-O-methyl-α-D-glucopyranos-6-ylimino)-D-glucitol, also known as camiglibose;

1,5,9,11,14-pentahydroxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenzo[a]naphthacene-2-carboxylic acid, also known pradimicin Q;









also known as trestatin A;

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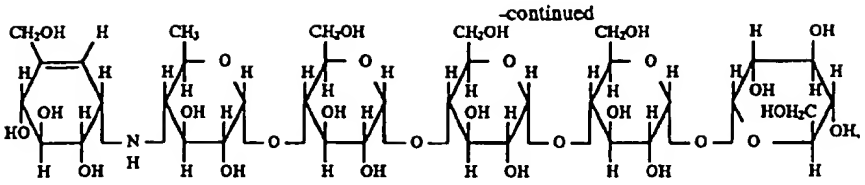
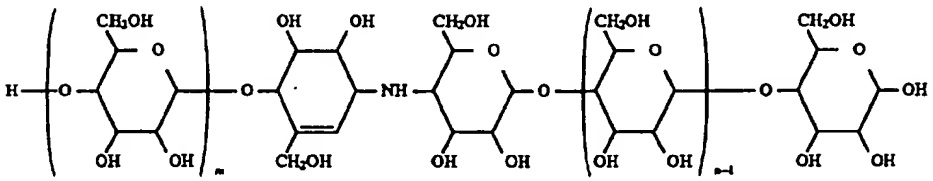


also known as trestatin B:

[I]



wherein m is an integer of 0 to 8, n is an integer of 1 to 8 and m+n is an integer of 1 to 8, also known as adiposine; and 1,2-dideoxy-2-[2(S),3(S),4(R)-trihydroxy-5-(hydroxymethyl)-5-cyclohexen-1(S)-ylamino]-L-glucopyranose, also known as salbostatin.

Examples of known lipase inhibitors are:

(2S,3S ,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, also known as tetrahydrolipstatin (previously also known as Orlistat);

(2S ,3S,5S,7Z, 10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone, also known as lipstatin;

1-(trans-4-isobutylcyclohexyl)-2-(phenylsulfonyloxy) ethanone, also known as FL-386;

4-methylpiperidine-1-carboxylic acid 4-phenoxyphenyl ester, also known as WAY-121898;

N-[3-chloro-4-(trifluoromethyl)phenyl-]N'-[3-(trifluoromethyl)-phenyl]urea, also known as BAY-N-3176;

N-formyl-L-valine-(S)-1 -[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]hexyl ester, also known as valilactone;

(2S,3S,5S,7Z,10Z)-5-[(S)-2-acetamido-3-carbamoylproplonyloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic lactone, also known as esterastin;

(3S,4S)-4-[(1S,5R,7S,8R,9R,E)-8-hydroxy 1,3,5,7,9-pentamethyl-6-oxo-3-undecenyl]-3-methyl-2-oxetanone, also known as ebelactone A;

(3S,4S)-3-ethyl-4-[(1S,5R,7S,8R,9R,E)-8-hydroxy-1,3,5,7,9-pentamethyl-6-oxo-3-undecenyl]-2-oxetanone, also known as ebelactone B; and

1,6-di(O-(carbamoyl)cyclohexanone oxime)hexane, also known as RHC 80267.

Biomasses or fermentation cakes which result in the fermentative manufacture of lipase inhibitors, such as, (2S,3S,5S, 7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1,3 acid lactone also known as lipstatin or (2S,3S,5S,7Z,10Z)-5-[(S)-2-acetamido-3-carbamoyl-propionyloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic lactone also known as esterastin, can also be used as the lipase inhibitor. The latter are described, for example, in EP-A 129 748 and U.S. Pat. No. 4,189,438.

It is known that either glucosidase inhibitors or amylase inhibitors or both, such as, O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)O-α-D-glucopyranosyl-(1→4)-D-glucose also known as acarbose, retard the digestion of carbohydrates.

It is also known that lipase inhibitors, such as, (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone also known as tetrahydrolipstatin, give rise to a partial inhibition of lipase in the intestine.

However, in monotherapy lipase inhibitors themselves in combination with a reduction diet generally bring about only a moderate weight loss and glucosidase and/or amylase inhibitors bring about practically no weight loss. It has now been surprisingly found that a combined use of a glucosidase and/or amylase inhibitor and a lipase inhibitor leads to a substantially greater weight loss than in the case of monotherapy. This has been demonstrated in the following test:

The test was carried out in two trial periods on two volunteers (A and B). The average daily calorie amounts of 2560 Kcal for A and 1850 Kcal for B were determined in a 7 day preliminary trial in which the volunteers took no medication. The volunteers were given 120 mg of (2S,3S,5S)-5-[(S)-2-formamido 4-methyl-is valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone also known as tetrahydrolipstatin and 100 mg of O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose also known as acarbose at each meal time in the subsequent 14 day main trial. A special diet was not adhered to and physical activities were reduced to a minimum. Here, as in the preliminary trial, the average daily calorie amounts of 2185 Kcal for A and 2050 Kcal for B were also ascertained. The weight loss of both volunteers will be evident from the following Table.

	Body weight	
Trial day	A	B
1	74.3	88.7
2	74.1	88.5
3	74.6	89.1
4	73.9	88.0
5	73.5	88.4
6	73.3	88.2
7	73.0	87.7
8	73.6	87.8
9	73.3	87.7
10	73.1	87.4
11	72.8	87.2
12	72.4	87.5
13	72.4	87.2
14	72.2	86.4
15	71.9	86.1
Weight loss	2.4	2.6

In comparison to the above result, the weight loss of patients in the case of monotherapy with tetrahydrolipstatin

(3×120 mg/day) in a placebo-controlled 12 weeks trial was on average 1.8 kg (i.e. 0.3 kg/14 days) (Int. J. Obesity 1992; 16 (Suppl. 1): 16, Abstr. 063).

In accordance with the invention, at least one but no more than two inhibitors of the glucosidase and/or amylase can be used in the form of pharmaceutical compositions in combination with a lipase inhibitor for the simultaneous, separate or chronologically spaced use in the treatment of obesity.

The use of O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α,)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)O-α-D-glucopyranosyl-(1→4)-D-glucose also known as acarbose and (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxyhexadecanoic 1,3 acid lactone also known as tetrahydrolipstatin is preferred.

The active ingredients are administered orally for the treatment of obesity.

They can be administered daily in dosages of about 0.003 mg to about 20 mg, preferably 0.015 mg to 10 mg, of glucosidase and/or amylase inhibitor and of about 0.15 mg to 20 mg, preferably 0.5 mg to 10 mg, of lipase inhibitor per kg body weight.

The compositions, in accordance with the invention, can be incorporated into standard pharmaceutical dosage forms, for example, they are useful for oral application with the usual pharmaceutical adjuvant material, for example, organic or inorganic inert carrier materials, such as, water, gelatin, lactose, starch, magnesium stearate, talc, gums, polyalkyleneglycols and the like. The pharmaceutical preparations can be employed in a solid form, for example, as tablets, capsules, or in liquid form, for example, as solutions, or emulsions. Pharmaceutical adjuvant materials can be added and include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

Solid dosage forms such as tablets and capsules conveniently contain per dosage unit about 0.2 mg to about 100 mg of glucosidase and/or amylase inhibitor and 10 mg to 200 mg of lipase inhibitor.

In addition to the treatment of obesity, the compositions or active substance combination, in accordance with the invention, can be used for the treatment and prevention of illnesses which frequently occur in association with overweight, such as diabetes, hypertension, hyperlipidemia and insulin-resistance syndrome.

In the case of all of these indications, the active substances can be used in the dosage ranges given above, with the individual dosage depending on the nature of the illness to be treated as well as on the age and condition of the patient and can be determined within the purview of the medical specialist.

The invention is illustrated in more detail by the following Examples.

Pharmaceutical compositions of the following composition are produced in a known manner:

EXAMPLE A

Soft gelatin capsules

	Amount per capsule
Tetrahydrolipstatin	60 mg
Medium chain triglyceride	450 µl
Acarbose	50 mg

EXAMPLE B

Hard gelatin capsules

Acarbose	25.0 mg
Tetrahydrolipstatin	30.0 mg
Cryst. lactose	37.0 mg
Microcrystalline cellulose	20.0 mg
Polyvinylpolypyrrolidone	8.5 mg
Sodium carboxymethylstarch	8.5 mg
Talc	4.5 mg
Magnesium stearate	1.5 mg
Capsule fill weight	135.0 mg

Tablets

Acarbose	25.0 mg
Tetrahydrolipstatin	30.0 mg
Anhydrous lactose	118.8
Microcrystalline cellulose	30.0
Polyvinylpolypyrrolidone	10.0
Carboxymethylcellulose	10.0
Magnesium stearate	1.2
Tablet weight	225.0 mg

EXAMPLE D

Tablets having controlled active substance release and increased residence time in the stomach

Acarbose	50.0 mg
Tetrahydrolipstatin	60.0 mg
Powd. lactose	70.0 mg
Hydroxypropylmethylcellulose	52.5 mg
Polyvinylpolypyrrolidone	7.5 mg
Talc	8.0 mg
Magnesium stearate	1.0 mg
Colloidal silicic acid	1.0 mg
Core weight	250.0 mg
Hydroxypropylmethylcellulose	2.5 mg
Talc	1.25 mg
Titanium dioxide	1.25 mg
Film coating weight	5.0 mg

EXAMPLE E

Powder for reconstitution

Acarbose	100.0 mg
Tetrahydrolipstatin	120.0 mg
Ethylvanillin	10.0 mg
Aspartame	30.0 mg
Sprayed skimmed milk powder	4740.0 mg
Total	5000.0 mg

The formulation of Examples A–E can be prepared by known methods.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 2

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 74 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Streptomyces tendae

(i x) FEATURE:
(A) NAME/KEY: Disulfide-bond
(B) LOCATION: 11..27

(i x) FEATURE:
(A) NAME/KEY: Disulfide-bond
(B) LOCATION: 45..73

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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Asp Thr Thr Val Ser Glu Pro Ala Pro Ser Cys Val Thr Leu Tyr Gln
1               5                  10                  15

Ser Trp Arg Tyr Ser Gln Ala Asp Asn Gly Cys Ala Glu Thr Val Thr
            20                  25                  30

Val Lys Val Val Tyr Glu Asp Asp Thr Glu Gly Leu Cys Tyr Ala Val
        35                  40                  45

Ala Pro Gly Gln Ile Thr Thr Val Gly Asp Gly Tyr Ile Gly Ser His
    50                  55                  60

Gly His Ala Arg Tyr Leu Ala Arg Cys Leu
65                  70
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: both

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Streptomyces sampsonii
(B) STRAIN: FH1656

(i x) FEATURE:
(A) NAME/KEY: Cross-links
(B) LOCATION: 8..25

(i x) FEATURE:
(A) NAME/KEY: Cross-links
(B) LOCATION: 9..26

(i x) FEATURE:

-continued

(A) NAME/KEY: Peptide
(B) LOCATION: 1..19

(i x) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 20..36

(i x) FEATURE:
(A) NAME/KEY: Cross-links
(B) LOCATION: 20..36

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Ala Thr Gly Ser Pro Ala Pro Asp Ser Asp Ala Val Thr Val Val Val
1               5                  10                  15

Gln Tyr Glu Gln Phe Ser Glu Val Cys Cys Gly Asn Arg Val Asp Thr
            20                  25                  30

Tyr Arg Trp Ser
        35
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We claim:

1. A pharmaceutical composition which comprises an effective amount of a lipase inhibitor and (a) a glucosidase inhibitor, (b) an amylase inhibitor or, (c) a glucosidase and amylase inhibitor, together with an inert carrier.

2. A pharmaceutical composition according to claim 1, wherein the daily dosage of a lipase inhibitor is 0.15 to 20 mg per Kg body weight and the daily dosage of said glucosidase inhibitor, amylase inhibitor or glucosidase and amylase inhibitor is 0.003 to 20 mg per Kg body weight.

3. A pharmaceutical composition according to claim 1, in the form of a solid dosage unit comprising per dosage unit 10 to 200 mg of a lipase inhibitor and 0.2 to 100 mg of said glucosidase inhibitor, amylase inhibitor or glucosidase and amylase inhibitor.

4. A pharmaceutical composition according to claim 2, wherein the lipase inhibitor is selected from the group consisting of (2S ,3S ,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1.3 acid lactone, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1.3 acid lactone, 1-(trans-4-isobutylcyclohexyl)-2-(phenylsulfonyloxy) ethanone, 4-methylpiperidine-1-carboxylic acid 4-phenoxyphenyl ester, N-[3-chloro-4-(trifluoromethyl)phenyl-N'-[3-(trifluoromethyl)phenyl]urea; N-formyl-L-valine-(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]hexyl ester, (2S ,3S, 5S,7Z,10Z)-5-[(S)-2-acetamido-3-carbamoylpropionyloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic lactone, (3S,4S)-4-[(1S,5R,7S,8R, 9R,E)-8-hydroxy-1,3,5,7,9-pentamethyl-6-oxo-3-undecenyl]-3-methyl-2-oxetanone, (3S,4S)-3-ethyl-4-[(1S, 5R, 7S,8R,9R,E)-8-hydroxy-1,3,5,7,9-pentamethyl-6-oxo-3-undecenyl]-2-oxetanone, and 1,6-di(O-(carbamoyl) cyclohexanone oxime)hexane.

5. A pharmaceutical composition according to claim 2, wherein the lipase inhibitor is (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1.3 acid lactone.

6. A method for treating obesity which comprises administering to a host in need of such treatment an effective amount of a lipase inhibitor and (a) glucosidase inhibitor, (b) amylase inhibitor, (c) or a glucosidase and amylase inhibitor.

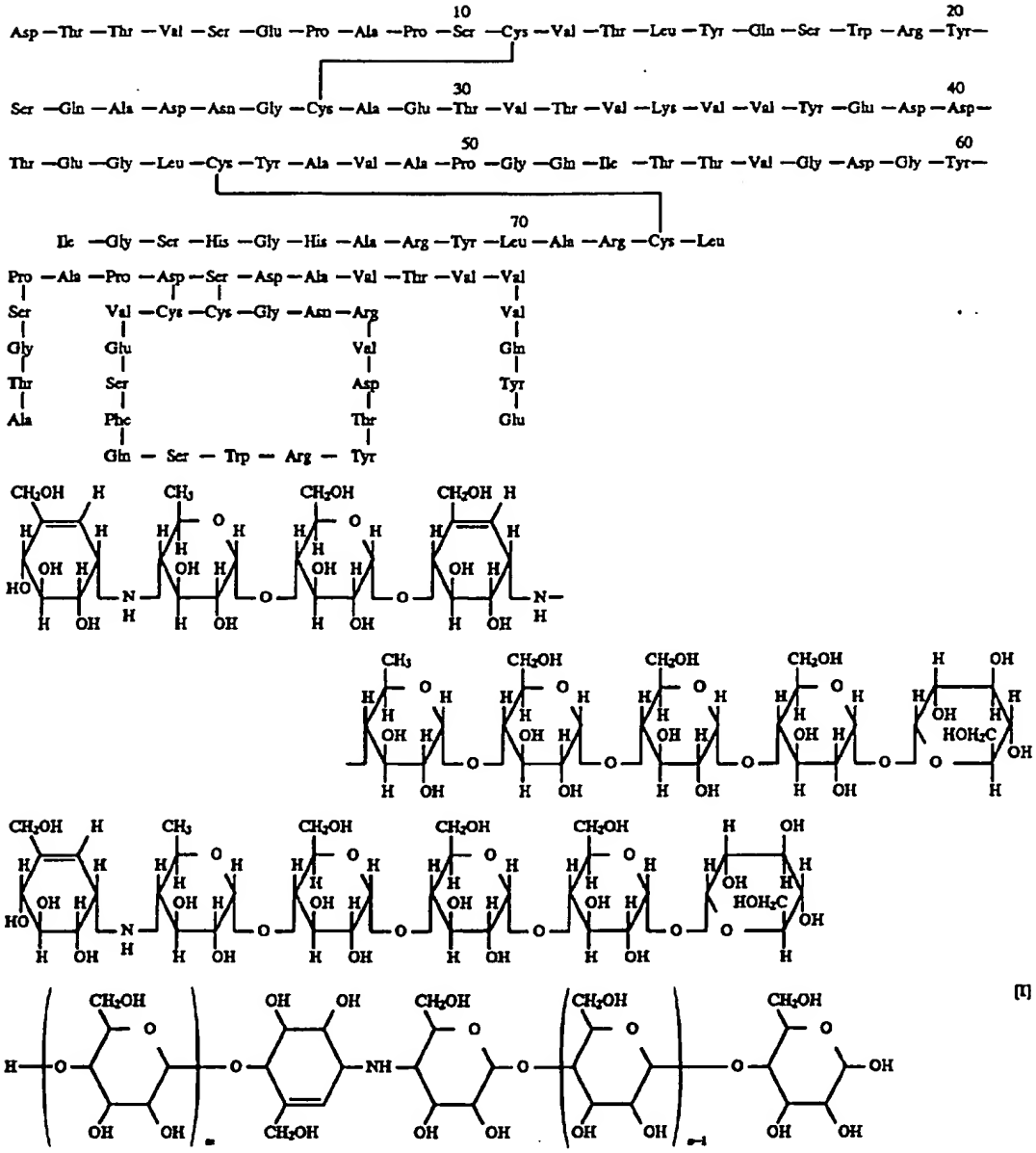
7. A method for treating obesity which comprises administering a lipase inhibitor and (a) a glucosidase inhibitor, (b) amylase inhibitor, or (c) a glucosidase and amylase inhibitor in a simultaneous, separate, or chronologically spaced manner.

8. A method according to claim 6, wherein the daily dosage of lipase inhibitor is 0.15 to 20 mg per Kg body weight and the daily dosage of said glucosidase inhibitor, amylase inhibitor or glucosidase and amylase inhibitor is 0.003 to 20 mg per Kg body weight.

9. A method according to claim 6, wherein the lipase inhibitor and (a) glucosidase inhibitor, (b) amylase inhibitor, or (c) glucosidase and amylase inhibitor are administered in a solid dosage unit comprising per dosage unit 10 to 200 mg of lipase inhibitor and 0.2 to 100 mg of the (a) glucosidase inhibitor, (b) amylase inhibitor, or (c) glucosidase and amylase inhibitor.

10. A method according to claim 7, wherein the lipase is inhibitor is selected from the group consisting of (2S,3S, 5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1.3 acid lactone, (2S,3S,5S, 7Z,10Z) -5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic 1.3 acid lactone, 1-(trans-4-isobutylcyclohexyl)-2-(phenyl-sulfonyloxy)ethanone, 4-methyl-piperidine-1-carboxylic acid 4-phenoxyphenyl ester, N-[3-chloro-4-(trifluoromethyl)phenyl-N'-[3-(trifluoromethyl)phenyl]urea, N-formyl-L-valine-(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]hexyl ester, (2S ,3S,5S ,7Z, 10Z)-5-[(S)-2-acetamido-3-carbamoyl-propionyloxy]-2-hexyl-3-hydroxy-7,10-hexadecadienoic lactone, (3S,4S)-4-[(1S,5R,7S,8R,9R,E)-8-hydroxy-1,3,5,7, 9-pentamethyl-6-oxo-3-undecenyl]-3-methyl-2-oxetanone, (3S,4S)-3-ethyl-4-[(1S,5R,7S, 8R,9R,E)-8-hydroxy-1,3,5,7, 9-pentamethyl-6-oxo-3-undecenyl]-2-oxetanone, and 1,6-di (O-(carbamoyl)cyclohexanone oxime)hexane.

11. A pharmaceutical composition according to claim 2, wherein the (a) glucosidase inhibitor, (b) amylase inhibitor or (c) glucosidase and amylase inhibitor is selected from the group consisting of O-4,6-Dideoxy-4-[[[1S-(1α,4α,5β,6α)] -4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl] amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose, 2(S),3(R),4(S),5(S)-tetrahydroxy-N-[2-hydroxy-1-(hydroxymethyl)-ethyl]-5-(hydroxymethyl)-1(S)-cyclohexamine, 1,5-dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol,1,5-dideoxy-1,5-[2-(4-ethoxy-carbonylphenoxy)ethylimino]-D-glucitol, 2,6-dideoxy-2,6-imino-7-(β-D-glucopyranosyl)-D-glycero-L-gulo-heptitol, 1,5-dideoxy-1,5-(6-deoxy-1-O-methyl-α-D-glucopyranos-6-ylimino)-D-glucitol,



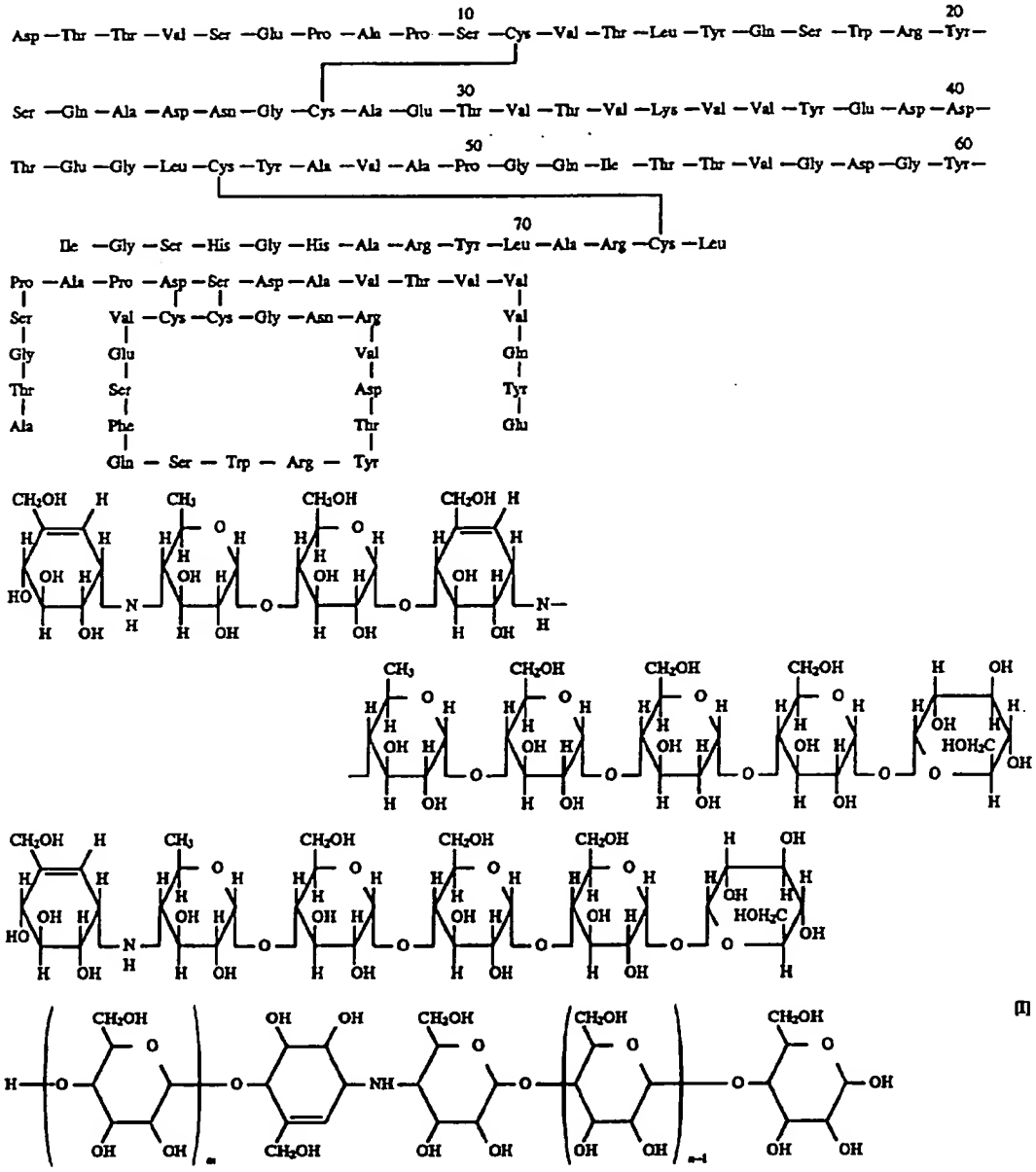
[I]

wherein m is an integer of 0 to 8, n is an integer of 1 to 8 and m+n is an integer of 1 to 8,

1,5,9,11,14-pentahydroxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenzo[a]naphthacene-2-carboxylic acid, and 1,2-dideoxy-2-[2(S),3(S),4(R)-trihydroxy-5-(hydroxymethyl)-5-cyclohexen-1(S)-ylamino]-L-glucopyranose.

12. A pharmaceutical composition according to claim 2, wherein the (a) glucosidase inhibitor, (b) amylase inhibitor, or (c) glucosidase and amylase inhibitor is O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose.

13. A method according to claim 7, wherein the (a) glucosidase inhibitor, (b) amylase inhibitor, or (c) glucosidase and amylase inhibitor is selected from the group consisting of O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose, 2(S),3(R),4(S),5(S)-tetrahydroxy-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-(hydroxymethyl)-1(S)-cyclohexamine, 1,5-dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol,1,5-dideoxy-,1,5-[2-(4-ethoxy-carbonylphenoxy) ethylimino]-D-glucitol, 2,6-dideoxy-2,6-imino-7-(β-D-glucopyranosyl)-D-glycero-L-gulo-heptitol, 1,5-dideoxy-,1,5-(6-deoxy-1-O-methyl-α-D-glucopyranos-6-ylimino)-D-glucitol.



wherein m is an integer of 0 to 8, n is an integer of 1 to 8 and m+n is an integer of 1 to 8, 1,5,9,11,14-pentahydroxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenzo[a]naphthacene-2-carboxylic acid, and 1,2-dideoxy-2-[2(S),3(S),4(R)-trihydroxy-5-(hydroxymethyl)-5-cyclohexen-1(S)-ylamino]-L-glucopyranose.

14. A method according to claim 7, wherein the (a) glucosidase inhibitor, (b) amylase inhibitor, or (c) glucosidase and amylase inhibitor is O-4,6-dideoxy-4-[[[1S-(1α, 4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose.

15. A pharmaceutical composition which comprises an effective amount of (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 and lactone; O-4,6-dideoxy -4-[[[1S-(1α4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose and an inert carrier.

16. A pharmaceutical composition according to claim 15, wherein the daily dosage of (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone is 0.15 to 20 mg per kg body weight and the daily dosage of O-4,6-dideoxy-4-[[[1S-(1α, 4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose is 0.003 to 20 mg per kg body weight.

17. A pharmaceutical composition according to claim 15, in the form of a solid dosage unit comprising per dosage unit 10 to 200 mg of (2S,3 S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone and 0.2 to 100 mg of O-4,6-dideoxy- 4-[[[1S-(1α,4α,

5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose.

18. A method for treating obesity which comprises administering to a host in need of such treatment an effective amount of (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone and O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose.

19. A method for treating obesity which comprises administering to a host in need of such treatment (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone and O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose in a simultaneous, separate, or chronologically spaced manner.

20. A method according to claim 18, wherein the daily dosage of (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone is 0.15 to 20 mg per kg body weight and the daily dosage of O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose is 0.003 to 20 mg per kg body weight.

21. A method according to claim 18, wherein (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone and O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose are administered in a solid dosage unit comprising per dosage unit 10 to 200 mg of (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone and 0.2 to 100 mg of O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4) O-α-D-glucopyranosyl-(1→4)-D-glucose.

* * * * *

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,707	04/10/2001	James U. Morrison	26017-3	1778

7590 07/09/2002

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EXAMINER
WHITE, EVERETT NMN

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,707	MORRISON, JAMES U.	
	Examiner	Art Unit	
	EVERETT WHITE	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

2. Claims 1-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Patel et al (US Patent No. 6,309,663).

Applicants claim a method for producing an extended-release composition comprising mixing acarbose with a sustained release matrix to create said composition.

The Patel et al patent discloses preparation of pharmaceutical compositions that comprises mixing surfactants with a hydrophilic therapeutic agent (see abstract), whereby the hydrophilic therapeutic agent may be selected as acarbose (see column 31, lines 57 and 58). Patel et al discloses that the pharmaceutical compositions may be in dosage forms, whereby the dosage form may be formulated as a tablet (see column 38, lines 1-3) as mentioned in instant Claim 2. The Patel patent discloses that the dosage form can be designed for extended release, which can be effected by a coated matrix composition. See the 3rd paragraph of column 38 and the first paragraph of column 40 for examples of cellulose derivatives that can be used to form the coating composition that include ethyl cellulose, hydroxpropyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose phthalate, and hydroxypropyl methyl cellulose succinate. These cellulose derivatives

encompass the subject matter of instant Claims 11 and 14. The Patel et al patent further discloses the present of other additives in the pharmaceutical compositions that include fillers and lubricants (see column 36, 4th paragraph) as set forth in instant Claims 5 and 7. The Patel et al patent discloses that pharmaceutically acceptable bases such as magnesium aluminum silicate and synthetic aluminum silicate (see column 37, lines 2 and 3) may be added to the composition, which fall within the broadly recited colloidal silica that is set forth in instant Claims 6 and 8. See Table 18 in column 23 of the Patel et al patent whereby sodium lauryl sulfate and sodium stearyl fumarate may be included in the pharmaceutical composition of the Patel et al patent, which are also set forth in instant Claim 9. The Patel et al patent further discloses magnesium stearate as part of the pharmaceutical composition, which is disclosed in instant Claim 10. In column 54, line 26, Patel et al discloses that the amount of acarbose present in the composition thereof ranges from 50 to 100 mg, which is within the range of the amount of acarbose set forth in instant Claim 4 and also fall within the 20% to about 40% range of the tablet set forth in instant Claim 3. The above describe preparation of the pharmaceutical composition of the Patel et al patent that comprises mixing acarbose and a coating anticipates the instantly claimed method for producing an extended-release composition comprising mixing acarbose with a sustained release matrix to create a composition.

3. Claims 15-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Patel et al (US Patent No. 6,309,663).

Applicants claim a chemical composition comprising acarbose and a sustained release matrix.

The Patel et al patent discloses a pharmaceutical composition that comprises surfactants and a hydrophilic therapeutic agent (see abstract), whereby the hydrophilic therapeutic agent may be selected as acarbose (see column 31, lines 57 and 58). Patel et al discloses that the pharmaceutical compositions may be in dosage forms, whereby the dosage form can be designed for extended release, which can be effected by a coated matrix composition (see column 38, 2nd paragraph). See the 3rd paragraph of

column 38 and the first paragraph of column 40 for examples of cellulose derivatives that can be used to form the coating composition that include ethyl cellulose, hydroxpropyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose phthalate, and hydroxypropyl methyl cellulose succinate. These cellulose derivatives encompass the subject matter of instant Claims 24-27. The Patel et al patent further discloses the present of other additives in the pharmaceutical compositions that include fillers and lubricants (see column 36, 4th paragraph) as set forth in instant Claims 18 and 20. The Patel et al patent discloses that pharmaceutically acceptable bases such as magnesium aluminum silicate and synthetic aluminum silicate (see column 37, lines 2 and 3) may be added to the composition, which fall within the broadly recited colloidal silica that is set forth in instant Claims 19 and 21. See Table 18 in column 23 of the Patel et al patent whereby sodium lauryl sulfate and sodium stearyl fumarate may be included in the pharmaceutical composition of the Patel et al patent, which are also set forth in instant Claim 22. The Patel et al patent further discloses magnesium stearate as part of the pharmaceutical composition, which is disclosed in instant Claim 23. In column 54, line 26, Patel et al discloses that the amount of acarbose present in the composition thereof ranges from 50 to 100 mg, which is within the range of the amount of acarbose set forth in instant Claim 17 and also fall within the 20% to about 40% range of the composition set forth in instant Claim 16. The above describe pharmaceutical composition of the Patel et al patent comprising acarbose and a coating anticipates the instantly claimed chemical composition comprising acarbose and a sustained release matrix.

4. Claims 28-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Bremer et al (US Patent No. 5,643,874).

Applicants claim a method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient.

The Bremer et al patent discloses glucosidase and/or amylase inhibitors that can be manufacture as pharmaceutical compositions for the combined use with a lipase inhibitor in the treatment of obesity (see column 1, line 27 and column 2, lines 1-3). The

Bremer et al patent discloses that the glucosidase and/or amylase inhibitor may be selected as acarbose (see column 2, lines 5-12). The Bremer et al patent discloses that the acarbose may be present in tablets that have controlled active substance release and increase residence time in the stomach (see Example D in column 6) which is within the meaning of the phrases "delayed release matrix" and "sustained release matrix" that is set forth in instant Claims 29 and 30. Example D discloses that the tablet comprises 50 mg of acarbose, which covers the amount of acarbose set forth in instant Claims 31 and 32. Example D sets forth the tablet as further comprising hydroxypropylmethycellulose, which is analogous to the hydroxypropylmethylcellulose that is disclosed in instant Claim 39; magnesium stearate, which is analogous to the magnesium stearate set forth in instant Claims 35 and 38; colloidal silicic acid, which is analogous to the colloidal silica set forth in instant Claim 36; and hydroxypropylmethylcellulose that is part of the coating film, which is analogous to the subject matter of instant Claims 40 and 41. See column 5, 6th paragraph, whereby the Bremer et al patent discloses the compositions thereof as being useful for oral application with the usual pharmaceutical adjuvant material, for example, organic or inorganic inert carrier materials, such as water, gelatin, lactose, starch, talc, gums, polyalkyleneglycols and the like, and Bremer et al discloses that the pharmaceutical adjuvant materials include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers, which are analogous to the broadly claimed filler, glidant, and lubricant that are set forth in instant Claims 33-35. The above describe method for treating obesity of the Bremer et al patent anticipates the instantly claimed method of treating a patient to stimulate weight loss.

5. Claims 15-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bremer et al (US Patent No. 5,643,874).

The composition used to treat obesity in the Bremer et al patent as describe in the above rejection also covers the composition set forth in Claims 15-27 of the instant application. Accordingly, Claims 15-27 also are rejected under 35 U.S.C. 102 as being anticipated by the Bremer et al patent.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 28-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bremer et al (US Patent No. 5,643,874) in view of Patel et al (US Patent No. 6,309,663).

Applicants claim a method of treating a patient to stimulate weight loss comprising administering an acarbose formulation to the patient.

The Bremer et al patent discloses glucosidase and/or amylase inhibitors that can be manufacture as pharmaceutical compositions for the combined use with a lipase

inhibitor in the treatment of obesity (see column 1, line 27 and column 2, lines 1-3), whereby the glucosidase and/or amylase inhibitor may be selected as acarbose (see column 2, lines 5-12). The information disclosed in the Bremer et al patent with regard to the treatment of obesity is substantially similar to the instantly claimed method of treating a patient to stimulate weight loss except for the limitation in instant Claim 42 whereby the coating used in the instant claimed method is a cellulose ether-based coating in combination with ethyl cellulose. The Patel et al patent shows that coatings that are cellulose ether–base coating in combination with ethyl cellulose is known in the art. See the first paragraph of column 40, which discloses coatings that may comprise cellulose derivatives including ethyl cellulose. See line 31 of column 40 whereby the Patel patent discloses combinations of the above materials can also be used which include ethyl cellulose and cellulose ether derivatives. The coatings disclosed in the Patel patent may be used to coat acarbose containing compositions. See column 31, lines 57 and 58 of the Patel patent whereby acarbose is a preferred hydrophilic therapeutic agent. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute coating used to coat the pharmaceutical composition used to treat obesity of the Bremer et al patent with a coating of cellulose ether-based in combination with ethyl cellulose in view of the recognition in the art, as evidenced by the Patel patent at lines 26-31 of column 39, that coatings of cellulose derivatives that may comprise ethyl cellulose allows for balancing enhancement effectiveness, active protection, and safety liability through coating controlled dilution of the hydrophilic therapeutic agent, upon administration through delayed release or sustained release.

Summary

8. All the pending claims are rejected.

Examiner's Telephone Number, Fax Number, and Other Information

9. For 24 hour access to patent application information 7 days per week, or for filing applications, please visit out website at **www.uspto.gov** and click on the button "Patent Electronic Business Center" for more information.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Everett White whose telephone number is (703) 308-4621. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter, can be reach on (703) 308-4532. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

E.White

JAMES O. WILSON
PRIMARY EXAMINER
Technology Center 1600